NOVEMBER 1954

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

WILLIAM B. CASTLE

CHESTER SCOTT KEEFER

RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

Transcription of a Panel Meeting

CHARLES RAGAN THEODORE BAYLES
EDWARD E. FISCHEL JOSEPH LEE HOLLANDER
T. DUCKETT JONES

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JOHN F. FULTON
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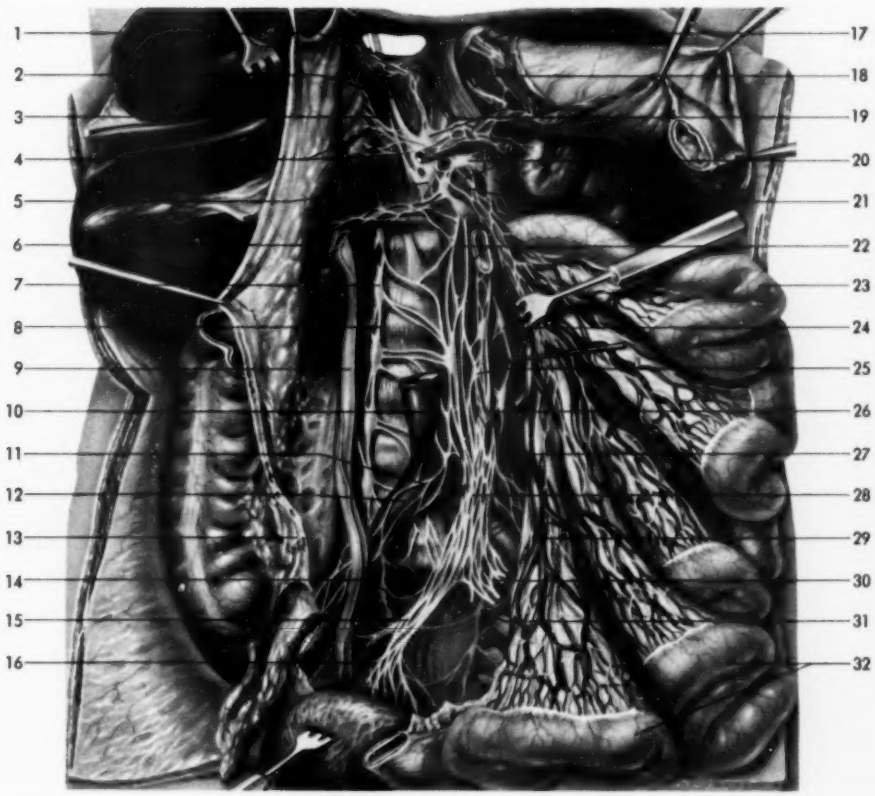

1 Phrenic ganglion and plexus
2 Greater splanchnic nerve
3 Lesser splanchnic nerve
4 Suprarenal plexus
5 Aorticorenal ganglion
6 Right renal artery and plexus
7 Right lumbar sympathetic ganglion
8 Right sympathetic trunk
9 Ureter
10 Vena cava
11 Iliac plexus
12 Right common iliac artery
13 Mesocolon (cut)
14 Right sacral sympathetic ganglion
15 Right pelvic plexus
16 Pudendal plexus
17 Left vagus nerve
18 Right vagus nerve
19 Celiac plexus and right celiac ganglion
20 Superior mesenteric ganglion and plexus
21 Left celiac ganglion; superior mesenteric artery
22 Abdominal aortic plexus
23 Jejunum
24 Left lumbar sympathetic ganglion
25 Inferior mesenteric ganglion
26 Inferior mesenteric plexus
27 Left sympathetic trunk
28 Hypogastric plexus
29 Branches of superior mesenteric artery and vein
30 Left pelvic plexus
31 Left sacral sympathetic ganglion
32 Ileum

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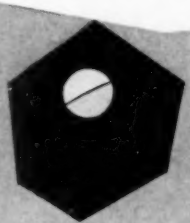

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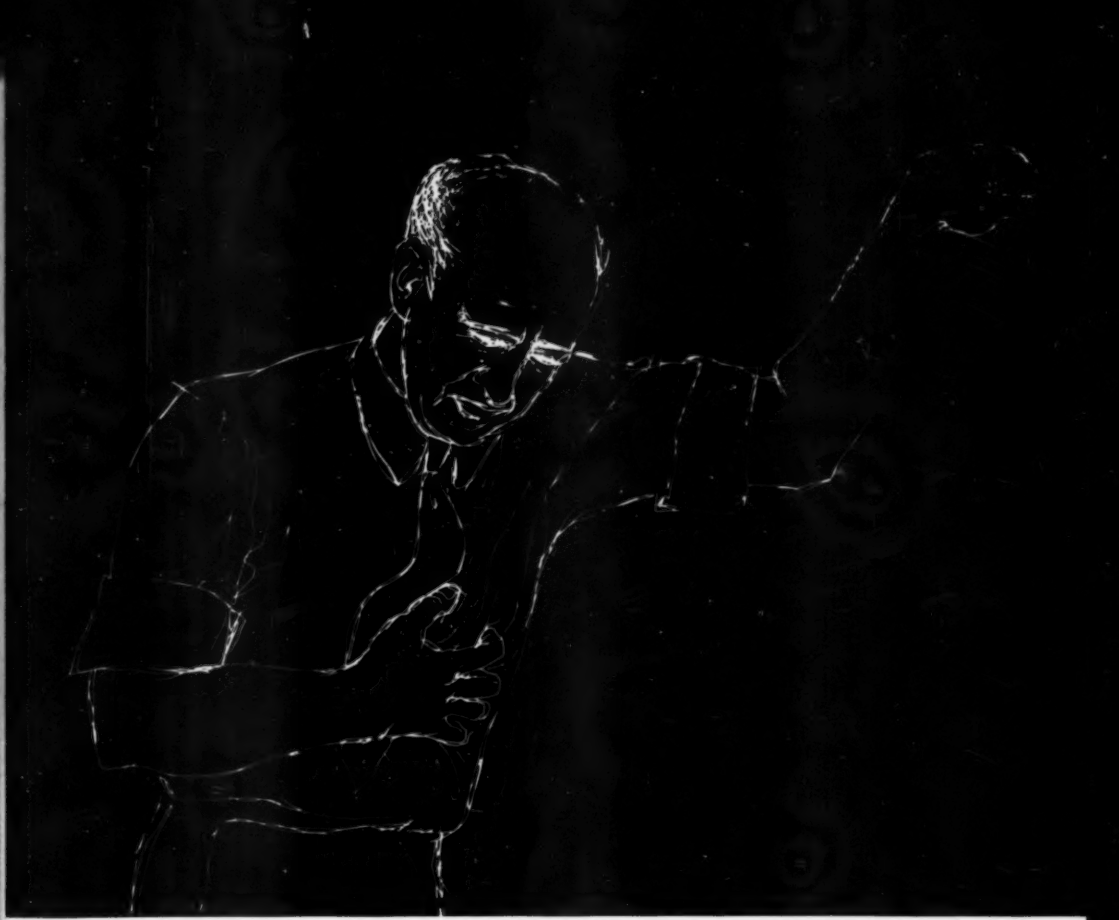

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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: N. Y. State J. Med. *52*:2012 (Aug. 15) 1952.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL 30, NO. 11 NOVEMBER 1954

ERYTHROPOIESIS: NORMAL AND ABNORMAL*

The Ludwig Kast Lecture†

WILLIAM B. CASTLE

Professor of Medicine, Harvard University; Director, Thorndike Memorial Laboratory; and Director, Second and Fourth Medical Services, Boston City Hospital

ERYTHROPOIESIS, the making of red blood cells, is in essence the production and packaging of hemoglobin. Because the evanescence of the porphyrins and the stability of iron with respect to the chemistry of hemoglobin production and degradation are admirably covered by the remarks of Dr. Granick[1] and of Dr. London,[2] I shall make only such reference to these subjects as may be required for the development of the more general topic assigned to me. Although of course qualitatively inseparable in the creation of the finished product, still the obvious differences in the size, color, and shape of the circulating red cell in various pathologic states indicate that red cell formation and hemoglobin production do not invariably proceed apace. The rates of both are normally subject to critical control, but in disease either may lag

* Presented at the 26th Graduate Fortnight of The New York Academy of Medicine, October 19, 1953.
† In honor of Dr. Ludwig Kast, who first suggested the Graduate Fortnight.

relative to the potential of the other in response to the normal or to an increased demand for circulating hemoglobin.

Normal Erythropoiesis

The manufacture of red cells begins early in life.[3-6] Hemoglobin-containing primitive erythroblasts develop within blood vessels when the human embryo is but two to five millimeters in length. By the fourth month of fetal life the liver is the chief site of red cell formation to be superseded after the fifth month at an accelerating rate by red cell production within the bone marrow cavities. At birth the marrow throughout the skeleton is fully active in the production of red cells containing fetal type hemoglobin, and the extramedullary sites have nearly vanished. Moreover, red cell formation has now become extravascular and thereafter throughout life it so remains and is confined to the bone marrow unless, with disease, the liver and spleen and sometimes the lymph nodes resume the erythropoietic function lost before birth. Likewise, within a few months after birth, the fetal hemoglobin has largely become of the adult type and so persists unless certain kinds of disturbed erythropoiesis continue or develop.

In the maturing child by a process of replacement progressing centripetally both with respect to the skeleton as a whole and to its individual peripheral components "fatty" marrow replaces active erythropoietic marrow. In the adult the process of distal withdrawal of cellular marrow has reached completion and from now on erythropoiesis is normally confined to the skull, vertebrae, ribs, pelvis, and upper third of the humerus and femur. Even so the active bone marrow, occupying perhaps a half of the total marrow cavity of 3000 cc., comprises altogether an organ the size of the liver. Moreover, it possesses the capacity to enlarge in gross size and to increase its erythropoietic function under the stimulus of anemia if the essential building stones and catalysts for red cell and hemoglobin production are provided. This functional response is accomplished in three ways: 1) By enlargement of the active marrow at the expense of the fatty marrow both locally in the central portions of the skeleton and in a peripheral direction in the long bones; 2) by an increase in the total number of erythropoietic cells as well as in the proportion of the less mature progenitors; and finally 3) even by an encroachment of active marrow upon the surrounding cortex of the bones themselves. The first process has long been familiar to pathologists

at the autopsy table. The second has become well known to clinicians through study of biopsy specimens and the third determines for the radiologist the cortical thinning of long bones and the "hair-on-end" appearance of the skull in chronic hemolytic anemias of childhood.[7]

The process of erythropoiesis in bone marrow involves both growth and cell division. Normally the youngest erythropoietic cells present in considerable numbers are the polychromatophilic normoblasts. With chronically increased erythropoiesis basophilic normoblasts become frequent and occasional pronormoblasts appear. At one or more stages of cell division one portion of the divided cell must remain capable of redivision, the other must be able to differentiate further. In bone marrow preparations mitosis may be seen at all levels of cell differentiation but with increasing frequency in the later stages down to the polychromatic erythroblasts. Thereafter mitoses are not observed and the final conversion of the normoblast to the reticulocyte appears to involve a post-mitotic process in which the pyknotic nucleus is simply discarded. There is no longer doubt concerning the position of the reticulocyte as the immediate precursor of the adult red cell. Although it is not certain that all red cells enter the circulation as reticulocytes, the orderly fluctuations of these cells in the peripheral blood in relation to changes in the rate of erythropoiesis induced by experimental procedures or by clinical circumstances are well known.[8] Moreover, both cultures in vitro[9] and survival of transfused reticulocytes[10] demonstrate conversion of the reticulocyte into the adult cell type in the course of about five days.

Ultraviolet absorption microspectroscopy[4, 11] including the use of the reflecting microscope indicates the heavy concentration of ribose polynucleotides in the cytoplasm and nucleoli of the early pronormoblast. Desoxyribose nucleic acid is confined to the nuclear chromatin. These substances are responsible for the basophilia of the young erythroid cells seen with the Romanowsky stains. The subsequent appearance of polychromatophilia in the cytoplasm of the erythroblast indicates the beginning of the formation of the globin of hemoglobin which later combines with or forms heme groups on its surface. In the late normoblast with pyknotic nucleus, the hemoglobin concentration reaches 20 to 25 per cent. Its final rise to 33 per cent has been attributed to loss of the nucleus and shrinkage of the cell from a spherical to a biconcave adult form.

Some information is available about the time required for the maturation of the erythropoietic cells of the bone marrow. The entire process clearly occupies less than ten days. Thus the reticulocyte response of a healthy, predominantly normoblastic marrow to a severe hemorrhage usually begins by the third or fourth day. In pernicious anemia the period of maximum reticulocyte release into the peripheral blood occurs from four to six days after the injection of a highly effective liver preparation and presumably represents the time required for the maturation of the predominant megaloblasts and pronormoblasts of such marrows to reticulocytes. In the aplastic crisis of congenital hemolytic jaundice, the time from the reappearance of pronormoblasts in the marrow to the reappearance of reticulocytes in the peripheral blood has been observed to be from three to five days.[12] The formation of hemoglobin is morphologically prominent in the polychromatic normoblast and in normal man N_{15}-labeled heme appears in the circulating red cells within two days after the feeding of N_{15}-glycine.[13] Indeed the incorporation of glycine into heme occurs in vitro in peripheral blood samples containing reticulocytes but no normoblasts.[14]

Reticulocytes display other evidence of the terminal stages of the erythropoietic process. Cytoplasmic polychromatophilia of these cells, visible with Romanowsky dyes, is presumably a residual of the ribose nucleoproteins that are so abundant in the pronormoblast. Brilliant cresyl blue, used supravitally, precipitates this material as the granular network characteristic of the reticulocyte. Reticulum may be similarly demonstrated in the hemoglobin-containing cytoplasm of pyknotic normoblasts from bone marrow preparations. Such normoblasts also contain iron-staining granules in their cytoplasm.[15, 16] These are less numerous in the reticulocytes and are usually absent from the mature circulating erythrocytes except in conditions of disturbed erythropoiesis or following splenectomy when it appears that the metabolic processes leading to the disappearance of these iron-staining granules may fall behind the cell-launching program.[15]

The red cell, instead of a hemoglobin solution, is no doubt an essential feature of oxygen transport in animals with a rapid circulation and a relatively high capillary pressure especially in such regions as the renal glomerulus. Under normal circumstances, once in the circulation, it survives from 100 to 120 days. During this period processes within the cell protect the hemoglobin from oxidation,[17] and factors encoun-

tered in the active circulation serve to maintain the energy essential to the preservation of its envelope.[18] Eventually the red cell becomes mechanically fragile[19] or otherwise defective as a result of some process closely related to its chronological age, and is destroyed. When the duration of life of the red cell is chronically shortened either as a result of intracorpuscular or of extracorpuscular abnormalities, the resulting lowering of the circulating hemoglobin concentration stimulates the bone marrow to an increased erythropoietic effort. With an average cell life of only fifteen days the circulating hemoglobin level is maintained at an only slightly reduced level by a 6 to 8 fold increase in the erythropoietic output.[20] With a red cell survival of only five days the output is even greater, but severe anemia is present. Thus, as shown by Robscheit-Robbins and Whipple,[21] with experimentally bled animals given adequate dietary building stones for hemoglobin production, the more anemic animals make more hemoglobin than the less anemic. This illustrates Cannon's principle of homeostasis for the erythropoietic mechanism. A steady state will be reached at any hemoglobin level when red cell production equals destruction. As logical corollaries, it must be assumed that no increase in erythropoiesis above the normal rate can occur without the stimulus of some anemia, however slight; and that, aside from polycythemia, it is impossible for a marked increase in the rate of red cell production to take place except in response to a marked reduction of the concentration of circulating hemoglobin.

The information concerning the nature of the stimulus to increased erythropoiesis resulting from anemia has recently been carefully reviewed by Grant and Root.[22] In both animals and in man when the amount or tension of the oxygen carried by the arterial blood is reduced, erythropoiesis becomes increased within a few days. This change in the arterial blood may result from red cell loss or destruction, from defective oxygenation of a normal amount of circulating hemoglobin as a result of high altitude, or of heart or lung disease, or from conversion of part of the circulating hemoglobin into compounds that do not readily accept and release oxygen such as methemoglobin or carboxyhemoglobin. Moreover, increased erythropoiesis is induced by cobalt which in biologically active amounts does not alter detectably the spectroscopic or physical properties of circulating hemoglobin but which, interestingly enough, under in vitro conditions does form complexes with oxygen and certain amino acids which are difficult of dissociation.[22, 23]

An increase in the amount or tension of the oxygen carried in the arterial blood of animals or man has the opposite effect, whether induced by breathing high concentrations of oxygen[22, 24] or by transfusion of red cells to polycythemic levels.[25] Oxygen administration results in a fall of reticulocytes and a decline in the level of circulating hemoglobin together with some depression of erythroid elements in the marrow. This is especially noticeable when the rate of erythropoiesis is rapid as in a chronic hemolytic anemia.[24] Multiple transfusions have similar effects until such time as the artificial elevation of the circulating hemoglobin level has disappeared. Thus the oxygen content of the arterial blood is closely related to the regulation of both increased erythropoietic effort and the ceiling for the circulating hemoglobin so achieved. In certain phases of the recovery of hypochromic anemia with iron therapy it can be observed that accelerated erythropoiesis ceases only when the hemoglobin reaches a normal value, which for the red cells may have been exceeded some time before.[26, 27] Thus, as to be expected from its close relation to oxygen tension, erythropoiesis is controlled not by the level of red cells but by the level of circulating hemoglobin.

Nature's seemingly carefully protective anatomical arrangements for erythropoiesis to take place within a rigid bony shell complete except where penetrated by a few blood vessels and nerves suggests at once a device for assuring relatively constant flow of blood perfusing the marrow cavity. The reciprocal relation between cellular and fatty marrow implies that the marrow cavity is at all times filled with incompressible liquids or solids. Indeed, in acute leukemia the rapid growth of cells may actually painfully raise the intramedullary pressure.[28] Consequently, under normal circumstances the hemoglobin concentration, rather than the rate of blood flow, would seem to determine the amount of oxygen brought to a given unit of marrow during a given interval of time.[3] If, then, the erythropoietic cells of the bone marrow were directly responsive to the stimulus of arterial anoxia (which seems at least indirectly effective in this fashion), each unit of bone marrow would appear to be provided with a self-contained local homeostatic mechanism capable of sharing equally with other units the work of erythropoiesis. Nevertheless, despite such suggestive appearances, direct measurements by needle puncture of the oxygen saturation of the blood perfusing the active marrow in anemic animals or men have failed to show consistent decreases.[22] Moreover, although there seems to be no

apparent need for such a device, convincing positive evidence has at last been presented for an indirect humoral effect on erythropoiesis. Thus, parabiotic rats develop a similar degree of normoblastic hyperplasia of the bone marrow when only one breathes air with lowered oxygen tension.[29] Again, Erslev[30] has recently shown that in both rabbits and monkeys the serum of animals rendered chronically anemic by bleeding contains a non-dialyzable substance that will cause reticulocyte responses and increases in circulating hemoglobin when injected intravenously into normal recipients. It is even claimed that nursing mice kept at low oxygen tension except when suckling their young, secrete in the milk a substance that causes polycythemia in the nurslings.[22] In a remarkable patient with polycythemia secondary to reverse flow in a patent ductus arteriosus the blood flowing to the head and sternal marrow contained normal amounts of oxygen while that going to the lower part of the body including the marrow of the iliac crest did not. However, the iliac marrow was less cellular than the sternal.[31] Less convincing evidence describes the central nervous system or even samples of blood rendered anoxic in vitro as sources of this erythropoietic humor. However, unless the blood itself is a self-contained system, the amount of oxygen per minute brought to some regulatory tissue by the blood must, somewhere in the body, be closely related to its hemoglobin content, for there, its oxygen content must be sampled by the regulatory tissue with precision. Perhaps the bone marrow provides the constancy of environment necessary for this more limited purpose or perhaps the humoral erythropoietic factor is, like the x-ray-shielded tissue factor of Jacobson,[32] only an emergency mechanism.

The spleen has long been considered to have an influence upon erythropoiesis; and this is manifestly so in instances of severe hemolytic anemia in which the spleen plays a major role in red cell destruction. Here, however, the increased red cell formation manifest by reticulocytosis and accompanied by the changes in bone marrow morphology and function already described is not demonstrably other than the indirect result of the hemolytic influence of the spleen, and is the direct result only of the severe anemia. When the spleen is removed and the anemia is abolished, the marrow reverts to a normal state because the anemic stimulus to erythropoiesis no longer exists. Similar normalization of the bone marrow would have resulted from the elimination of any other type of anemia unassociated with continuing primary marrow

dysfunction. Consequently, the major effect of the presence of the spleen on erythropoiesis in hemolytic anemias is indirect and so clearly non-specific.

On the other hand, splenectomy in normal animals and in man may have a small and direct effect upon erythropoiesis, perhaps especially with respect to the rate of hemoglobin production. In normal animals the anemia following splenectomy is at most slight, and may be no greater than that observed in sham-operated controls. However, in guinea pigs[33] as well as in dogs,[34] the red cells progressively decrease in osmotic fragility for a period of a few weeks after the spleen is removed. This change is associated with the appearance of "target" cells. These are also tangible evidence of the production of a "flattened" type of erythrocyte by the bone marrow, a phenomenon that may persist for many weeks. In man similar changes in the red cells are seen after splenectomy and in other clinical states as well, in which difficulty with hemoglobin production exists; for example, after hemorrhage and in sickle cell and Mediterranean anemias. Then, too, the appearance of adult circulating red cells containing iron-staining granules siderocytes) as well as nuclear remains (Howell-Jolly bodies) after splenectomy has often been assumed to be the result of the removal of the splenic filter. However, it has recently been shown that iron-containing granules are normally found in normoblasts and reticulocytes in the bone marrow in considerable numbers. Consequently, the evidence suggests that the spleen normally exerts a maturing influence upon the completion of the metabolism of iron and possibly the formation of hemoglobin.[15, 16] The effect of splenectomy is then perhaps in some way to delay the completion of this process which in turn may account for the slight hypochromia with flattening and decrease of osmotic fragility of the red cells resulting from splenectomy. Such changes, although the opposite of those of congenital hemolytic jaundice, do not imply, as is often supposed,[34] a "super-normal" survival time for the red cells of splenectomized patients. Finally, it should be mentioned that in certain patients with refractory anemia, hypocellular bone marrow and diminished ability to produce red cells, the removal of the spleen may actually increase the erythroid cellularity of the bone marrow and its rate of incorporation of radioactive iron into circulating hemoglobin.[35] These effects are, of course, the reverse of those that would have occurred had only an occult hemolytic process been diminished, and are

far less predictable.

Variations in the size, color and shape of the red cell reflect physiologic and pathologic alterations of the erythropoietic process. Thus, large cells are the descendants of large precursors in the bone marrow presumably when there is no delay in the hemoglobin forming process; and it has been shown that during active initial responses to blood loss or with continuing red cell lysis the red cells[36] and the marrow normoblasts may be larger than normal.[4] Macrocytosis is classically associated in pernicious anemia with a whole series of large erythropoietic marrow cells including megaloblasts, pronormoblasts and normoblasts.[4, 37] Actually macrocytosis of the more mature progenitors may occur to some extent in any type of anemia except those of iron deficiency, chronic infections, sicklemia, and thalassemia minor. In these last, some type of disturbance in hemoglobin formation exists, and the adult red cell is smaller than normal. The predominant marrow erythroid cell in iron deficiency is a small, pale normoblast with little or no cytoplasm.[38] Hypochromia is the hallmark of inadequate hemoglobin production whether as a result of iron deficiency, chronic infection, lead poisoning, or thalassemia. In the last, the variation in hemoglobin concentration of individual cells is striking. In congenital hemolytic jaundice the hemoglobin concentration may exceed the normal 33 per cent by as much as 5 per cent. The normal discoidal shape of the red cell allows it to be deformed in traversing narrow capillaries without the risk of rupture due to increase of the cell surface that would result were the cell spherical in form. The irregular and bizarre shaped red cells seen in certain anemias and at one time thought to be the result of fragmentation in the circulation probably are the progeny of abnormally shaped normoblasts. Except following extensive thermal burns, such red cells are less common in purely hemolytic anemias. With a diminished rate of hemoglobin synthesis, more than normally flattened red cells are formed with consequent decrease in "osmotic fragility." This characteristic is, in fact, not a measure of difference in osmotic behavior but of the difference between the actual volume of the cell and that of a sphere with equal surface. Thus, in hypotonic plasma equal volumes of different red cells swell equally.[39] The spheroidal cell of congenital hemolytic jaundice has the highest hemoglobin concentration of any kind of red cell. Probably for this reason it is the most nearly spherical, and consequently has the greatest "osmotic fragility." Other hereditary abnor-

malities of hemoglobin synthesis condition the extremely low hemoglobin concentration and flat cells of thalassemia and the orientation with anoxia of the abnormal hemoglobin molecules that causes sickling of the red cell.[40] These and other congenital defects of erythropoiesis are discussed by Dr. Watson.[41]

Abnormal Erythropoiesis

The nature of the active erythropoietic response in the anemias of red cell loss due to hemorrhage or hemolysis has already been described. When hemolysis is due solely to extracorpuscular factors without adverse effect on the bone marrow, the resulting anemia is due solely to the inherent limitations of the capacity of the bone marrow to produce red cells in response to a given degree of anemia. The limitations on erythropoiesis are similar when, as in the production of congenitally spherocytic red cells, the rate of hemoglobin formation is not recognizably interfered with, and the bone marrow produces red cells of abnormal susceptibility to lysis. Only in this indirect way does this constitute a form of deficient erythropoiesis. On the other hand, for example, with chronic bleeding, iron deficiency becomes a superimposed special limiting factor on the rate of erythropoiesis. Again, when as in the case of thalassemia, a congenital defect in the rate of hemoglobin production is also present, the erythropoietic capacity of the marrow is restricted by this special factor as well as by the inherent limitations of the normal organ. In pernicious anemia the situation is even more complex as here vitamin B_{12} deficiency results in a diminished rate of erythropoiesis that apparently produces qualitatively defective red cells which as weaklings must struggle to survive in an abnormally hostile environment.[42] This situation illustrates the inherently disastrous consequences of a disease process that interferes with the homeostatic mechanisms of erythropoiesis. Thus, if the degree of vitamin B_{12} deficiency both decreases the rate of red cell production and increases the rate of red cell destruction, an unstable equilibrium or vicious cycle is established. It is possible that this is the underlying cause of the classical tendency in pernicious anemia for the hemoglobin level to wax and wane dramatically.

The direct influence of various abnormal circumstances upon erythropoiesis will now be considered: nutritional deficiency, endocrine deficiency, toxic inhibition, and mechanical interference with bone marrow function. As a result of these disturbances, anemia results pri-

marily from a state of physiologic hypoactivity of the bone marrow; and this functional inadequacy may be reflected in the characteristics of the peripheral blood with respect to one or more of the principal circulating elements contributed to it by the bone marrow: red cells, granulocytes and platelets. Thus, for example, in chronic benzol poisoning or in pernicious anemia the reticulocytes are characteristically few as are the granulocytes and platelets. A corresponding hypocellularity of the germinal organ as in aplastic anemia is, however, by no means the rule. Indeed, in both conditions just cited an increase in erythroid cellularity with evidence of decrease in maturity is well known and has led to the concept of so-called "maturation arrest" or more accurately of "maturation delay" as an explanation of the diminished, but still perceptible, rate of red cell production.[4, 6, 37]

Nutritional deficiency of erythropoiesis: If animal experiments under highly specified nutritional conditions are interpreted as relevant to man, the dietary essentials for normal erythropoiesis are numerous and include minerals such as iron, copper, cobalt, and nickel, various amino acids, and vitamins such as pyridoxine, niacin, vitamin B_{12}, folic and ascorbic acids as well as possibly riboflavin, pantothenic acid, and thiamine.[43] Copper is known to be essential for iron absorption and may be an active catalyst in the formation of heme.[44] Only in ruminants does cobalt deficiency lead to a failure of adequate vitamin B_{12} synthesis by the bacteria of the rumen. Pyridoxine deficiency produces a severe disturbance in iron metabolism with hypochromic anemia associated with high serum and tissue iron levels and consequently with a tantalizing resemblance to thalassemia. With deficiency of vitamin B_{12} or folic acid, methyl donors such as choline and methionine or nucleic acid precursors such as uracil and thymine have sometimes been able to substitute partially for breaks in the metabolic chain leading to defective nucleoprotein synthesis.[37, 45] Lack of dietary protein, often mentioned as a cause of anemia in man, is better considered as a general index of malnutrition including an associated vitamin B_{12} or iron deficiency. Indeed, hemoglobin formation in hypochromic anemia in response to iron therapy will take place preferentially to serum protein formation in patients with exceedingly low protein intakes and serum protein levels.

Under clinical conditions in man, however, as emphasized by Dr. Wintrobe,[46] deficiency of very few substances becomes a limiting factor upon erythropoiesis: iron, folic acid (pteroylglutamic acid and its con-

jugates), ascorbic acid and vitamin B_{12}. These normal dietary components are not in any sense non-specific erythropoietic stimulants like cobalt which in pharmacologic (as opposed to trace) doses appears so to act possibly by producing histotoxic anoxia of the regulatory cells for erythropoiesis.[22, 23] Unlike cobalt too, none of the specific nutrients is hematopoietically effective in the non-anemic individual. Each is capable of enhancing red cell production only when specifically lacking in the anemic individual and, with the exception of folic and folinic acids in the presence of adequate ascorbic acid, none is completely interchangeable with another in producing such effects.[37, 45, 47, 48] When in the same patient, a macrocytic, hypochromic (dimorphic) anemia due to a combination of both vitamin B_{12} and iron deficiency develops, it is usually impossible to initiate erythropoiesis with iron until after vitamin B_{12} has been administered. This is presumably due to the fact that it is first necessary to abolish the vitamin B_{12} deficiency in order that the iron deficiency shall become the controlling nutritional defect in erythropoiesis.

Deficiency of vitamin B_{12}, folic acid, or ascorbic acid, alone or in combination, determines a diminished rate of red cell production accompanied by so-called megaloblastic erythropoiesis in the bone marrow. The marrow becomes intensely cellular and may expand to occupy the marrow spaces of much of the long bones. Unless perhaps with an associated iron deficiency, there is in vitamin B_{12} deficiency, evidence of an unusually rapid catabolism of heme precursors or possibly hemoglobin besides that present in the circulating red cells.[49]

These nutritional deficiencies may result directly from a dietary lack of animal protein (vitamin B_{12}) or from inadequate vegetable or animal sources (folic acid and ascorbic acid). In pernicious anemia a lack of vitamin B_{12} is chiefly conditioned by defective absorption from the small intestine. This results either from secretory failure of gastric intrinsic factor, a substance specifically facilitating the absorption of vitamin B_{12},[50, 51] or, as also in the defective absorption of folic acid, from innate small bowel disease. The intrinsic factor is thought to be mucoprotein in nature.[52, 53] The importance in man of intestinal bacteria (or larger parasites) in competing for or in providing additional sources of vitamin B_{12}, folic or folinic acids is uncertain. The demonstrated enhancement of erythropoiesis by antibiotics such as Aureomycin[54] or penicillin[55] may be specifically related to reduction in numbers or to

modification of the biosynthetic activities of the bacterial flora, or the effect may be non-specific by abolishing a source of unrecognized "intestinal poisoning" exerting an adverse influence similar to that of certain parenteral infections. Liver disease may also in some way interfere with the activity of folic acid.

The morphology of the bone marrow in each of these biochemical types of deficiency may be identical although a classical megaloblastic marrow is rarely found in clinical scurvy. The derangement is fundamentally one in which nuclear maturation lags behind cytoplasmic maturation.[4, 37] This characterizes the whole series of abnormal and large red cell precursors with relatively immature nuclear structure in pernicious and related anemias. Moreover, macrocytosis and abnormalities of the nuclear shape of the granulocytes are even more delicate indicators of deficiency; and immaturity of nuclear structure of megakaryocytes has been reported in pernicious anemia. Indeed, similar changes in other rapidly growing cell systems are produced by such deficiencies. Thus, Graham and Rheault[56] have shown that squamous and columnar epithelial cells exfoliated from the stomach or vagina of patients with pernicious anemia are large and display nuclear abnormalities. These disappear with vitamin B_{12} therapy. Similar findings have been noted in the small intestinal mucosa in folic acid deficiency.

Several observations suggest that the development of the predominantly megaloblastic bone marrow requires that, in addition to some degree of nutritional deficiency, a sufficient rate of cell division or growth be maintained. First, with any severe purely hemolytic anemia, there is a tendency to increased immaturity and some enlargement of the erythropoietic cells of the marrow.[4] Second, rapidly repeated serial transfusions of packed cells in pernicious anemia patients which raise the hemoglobin within ten days to normal levels markedly diminish the percentage of megaloblasts in the marrow.[57] Two patients treated in this way received insignificant amounts of vitamin B_{12}: less than a total of 0.4 μg. each. Their granulocyte and platelet levels were not altered until subsequently when liver extract was administered. Third, in a patient with congenital hypoplastic anemia, refractory to vitamin B_{12}, cortisone therapy has resulted in a marked increase in erythroid cellularity of megaloblastic type.[58] The anemia then responded to vitamin B_{12}. Finally, in occasional patients with early chronic myelogenous leukemia (myeloid metaplasia) and moderate anemia, the injection of

liver extract or of vitamin B_{12} has, in our experience, produced significant reticulocyte peaks. These were not followed by subsequent rises of red cell or hemoglobin levels. Thus, the degree of megaloblastosis in the marrow may not indicate a corresponding absolute reduction in serum or tissue vitamin B_{12} levels but may rather reflect the degree of vitamin B_{12} deficiency relative to the rate of reproduction of the erythroid cells of the marrow.

Although pernicious anemia is to a variable extent a hemolytic anemia, there is no doubt that erythropoiesis is also defective. Thus, the injection of a potent liver extract causes within forty-eight hours a rapid decrease in the number of megaloblasts and an increase in polychromatic normoblasts of the bone marrow[59] before any significant increase in peripheral red cell or hemoglobin levels has occurred. The subsequent reticulocyte response observed has now become a classical phenomenon. Moreover, similar effects upon local marrow morphology occur when a minute amount of vitamin B_{12} is instilled directly into the marrow cavity;[60] and have been claimed by some to occur in vitro with bone marrow cultures from pernicious anemia patients to which purified liver extract, folic or folinic acids,[61] or vitamin B_{12} have been added.[62]

Defective erythropoiesis due to vitamin B_{12} deficiency can be distinguished from that due to folic acid deficiency by serum levels of vitamin B_{12} or by the appearance of one or more reticulocyte responses during successive contiguous ten day periods of uniform daily exhibition of appropriate test substances. Thus, in this fashion, it can be shown that patients with pernicious anemia (serum vitamin B_{12} less than 100 micromicrograms per cc.)[63] respond initially to vitamin B_{12}, to folic acid or to the citrovorum factor. However, patients with folic acid deficiency (serum vitamin B_{12} normal) do not respond to vitamin B_{12} but do so to folic acid or to the citrovorum factor. Patients with clinical scurvy and macrocytic anemia (serum vitamin B_{12} normal) do not usually respond to ascorbic acid alone[64] but do respond partially to folic acid and more actively still when ascorbic acid is added to this regimen.[37, 65] With this last combination it can be shown that the excretion of citrovorum factor in the urine is strikingly increased, an observation which confirms for man the conclusion of workers with experimental animals or tissue slices that ascorbic acid is necessary in the animal in order that folic acid can be converted into its active metabolic form: folinic acid or the citrovorum factor.[47, 48]

The precise metabolic inter-relationships between pteroylglutamic acid and vitamin B_{12} are more obscure. However, based on indications supplied by microbial and animal studies, claims for their relevance have been presented before the court of last appeal: patients with vitamin B_{12} or folic acid deficiency. From observations and conclusions reached by Vilter and his associates,[45] the possible essential links in a metabolic chain which ends in the synthesis of nucleic acids have been described. Here folic acid, or more likely its active metabolite, folinic acid, or the citrovorum factor, catalyzes the formation of thymine and other essential purines and pyrimidines from intermediary compounds such as uracil. Vitamin B_{12} is involved at a subsequent stage in the formation of the nucleoside thymidine from thymine by the addition of the 5 carbon sugars, ribose and desoxyribose. In pernicious anemia this vitamin B_{12}-requiring reaction can be "forced" by the mass action of large amounts of folic acid until an extreme deficiency of vitamin B_{12} finally limits erythropoiesis severely. When folic (or presumably ascorbic) acid deficiency conditions a lack of folinic acid, the formation of thymine (5 methyl uracil) cannot be "forced" by even large doses of uracil unless methyl donors such as choline and methionine are also given. Because preformed thymine alone is rapidly effective, these substances are presumed to enhance the methylation of uracil to form this compound.

Deficiency of iron causes chiefly a diminished rate of hemoglobin production. The relatively unhampered production of red cells allows their number considerably to exceed the normally corresponding hemoglobin level in the peripheral blood. This of course, is the result of the reduced concentration of hemoglobin per red cell. The bone marrow becomes moderately increased in gross size and in erythroid cellularity chiefly at the level of the basophilic or polychromatophilic normoblasts.[38] Maturity of cytoplasm lags behind nuclear condensation and full cytoplasmic orthochromia of normoblasts does not develop. Many normoblasts display only a narrow rim of bluish-gray cytoplasm around a pyknotic nucleus. The serum iron level and the tissue iron stores[66] are, as measured by the estimation of the amount of iron-staining material in the reticuloendothelial cells of the bone marrow and of other tissues, greatly reduced. The absence of iron-staining granules in the normoblasts is an indication of still further iron depletion.[15] The administration of iron causes a reticulocyte response and a more rapid rate of increase of

hemoglobin than of red cells owing to the increment of red cells with a more nearly normal concentration of hemoglobin.[26]

Lack of available iron for erythropoiesis in adults results invariably from a positive external blood loss such as abnormal bleeding, menstruation, or pregnancy. In growing children, relative iron depletion occurs without external blood loss as a result of expansion of the circulating blood volume in which a constant hemoglobin concentration is normally maintained. In adults the intake of iron may fall behind even a moderately increased external loss for the reasons described elsewhere by Dr. Granick.[1] Thus, the conversion of the ferric iron of the food to ferrous iron required for its subsequent absorption may be impeded by lack of gastric hydrochloric acid or lack of weak organic acids or other reducing compounds in the food. Because iron absorption readily occurs in pernicious and in refractory hypoplastic anemias in which serum and tissue iron levels are not reduced,[67] it is doubtful that the ferritin level of the mucosal cells of the intestine directly controls iron absorption. In the absence of anemia, in hemochromatosis the ferritin mechanism of the small bowel seems unable to keep out the iron.

Endocrine deficiency of erythropoiesis: This alone is of little moment as a cause of abnormal erythropoiesis. However, when thyroid function is decreased either as a result of primary myxedema or of atrophy of the gland secondary to anterior pituitary failure, erythropoiesis is depressed although perhaps not out of proportion to the general lessened growth and oxygen consumption of the other tissues in the body. The trivial anemia is normochromic and normocytic or slightly macrocytic. The relatively few bone marrow biopsies reported indicate moderate erythroid hypocellularity without marked change in the type or proportions of the remaining cells. Some reports indicate more severe hypoplasia with increase of fat or of acellular material resembling fibrin.[68]

Bomford[69] has proposed that the hypofunction of the bone marrow is the result of a less than normal local anoxic stimulus to erythropoiesis resulting from the diminished oxygen consumption of the marrow erythroid cells. This theory would be valid irrespective of the location of the oxygen sensitive cells controlling erythropoiesis. In thyroidectomized animals and in myxedematous patients, reticulocyte responses and increased red cell and hemoglobin production follow the giving of thyroid extract. When, probably owing to the frequency of gastric

anacidity and the occasionally associated lack of intrinsic factor in myxedema, hypochromic anemia frequently and pernicious anemia infrequently is superimposed, the defective erythropoiesis and blood pictures typical of those conditions appear. Appropriate administration of iron[69] or of liver extract[70] prior to thyroid medication in such anemias causes typical erythropoietic responses in the peripheral blood. These at first are not manifestly less than in similar patients without myxedema, but hemoglobin regeneration levels off at about 70 or 80 per cent of normal values as in the uncomplicated case of myxedema. Adequate thyroid extract therapy may then cause a reticulocyte response and will in time abolish the anemia completely.

It appears, then, that thyroid hormone deficiency does not initially inhibit but later places a ceiling on the erythropoietic response. Animal experiments indicate that the normal sex differences in hemoglobin levels are the result of endocrine differences and can be reversed or modified by appropriate therapy.[22] Castration or estrogen therapy appears to lower the hemoglobin ceiling to approach the level. Corticosteroid therapy in man has some anti-anemic effect, but this is usually the indirect result of decreasing the rate of red cell destruction or of suppressing inflammatory tissue responses. The rare effect of cortisone in promoting erythropoiesis in refractory anemia has already been mentioned.[35, 38]

Toxic inhibition of erythropoiesis: This is thought to be the result of poisoning of the bone marrow by intoxicants of both external and internal origin. The first condition is represented by patients with "refractory anemia," many of whom give a suggestive history of exposure to benzol or other aromatic compounds in industry, home, or hospital.[71] The less than discriminating use of chloramphenicol supplies a recent illustration. Internal intoxication is probably the basis of the inhibition of erythropoiesis in chronic infections such as tuberculosis and osteomyelitis,[5] chronic metabolic or allergic disorders such as rheumatoid arthritis and uremia[72] and chronic intoxication due to widespread necrotic cancer or lymphoma.[73] Fever is not an essential factor.

The studies of Bomford and Rhoads,[71] as well as of others,[4] have disclosed that in refractory anemia, a similar normochromic, normocytic or moderately macrocytic anemia with granulocytopenia and thrombocytopenia may be associated with bone marrows of widely different microscopic appearance: hypocellular, partly mature and cellular, or

highly immature and highly cellular. Dacie's[4] detailed observations indicate that erythropoiesis is often arrested to a varying degree in the early stages of megaloblastic or pronormoblastic proliferation. Some of these cells may develop pyknosis of the nucleus and degenerate without further differentiation. The correlation between the severity of the anemia and the degree of immaturity of the marrow is reminiscent of appearances in pernicious anemia. At times the bone marrow may become less cellular and sometimes fibrotic. On the other hand, patients initially with hypocellular marrows may develop increased cellularity and eventually die of what appears to be leukemia.

It is not certain whether "toxicity" or "allergy" is the mechanism of the original insult.[74] Clinical and experimental evidence favor either. However, Bomford and Rhoads[71] demonstrated an increased excretion of coproporphyrins of type III as in lead and arsenic intoxication and in some types of liver disease. Because dietary deficiency was shown in experimental animals to cause increased susceptibility to amidopyrine and to indol (a substance formed by the action of intestinal bacteria on protein) they considered that refractory anemia might be due to a conditioned inability of the patient's liver to detoxify such substances either of endogenous or exogenous origin by one of several established mechanisms. This theory has even more to recommend it today. Thus, acute abstinence from chronic alcohol ingestion often results in a temporary reticulocyte rise in the macrocytic anemia associated with liver disease.[75] Antimetabolites such as folic acid antagonists are known within a few days to cause appearances in the erythroid cells of the marrow characteristic of prolonged dietary deficiency of folic acid[76] and so suggestive of the "megaloblastic" erythroid precursors of patients with refractory anemias. The unfavorable effects of blind intestinal loops upon erythropoiesis are again under study;[77] and antibiotics capable of altering the intestinal flora have been shown to cause increased erythropoiesis in pernicious anemia.[54, 55] Such observations bring the matter of "intestinal poisoning" again out of the discard. Finally, their hypothesis places the basic and continuing disturbance outside of the bone marrow and so disposes of the problem of understanding why the constantly renewed erythroid cells of the marrow do not "outgrow" their difficulty.

The anemia of chronic infection is mild but may become more severe, owing to the inability of the bone marrow to respond, if blood

loss occurs. In man the inhibitory effect of an acute infection upon erythropoiesis is readily observed—for example, during the reticulocyte response to liver therapy in pernicious anemia[3] or in the form of the so-called "aplastic crisis" of hemolytic anemias such as congenital hemolytic jaundice[12] or sickle cell anemia.[78] Extensive studies in experimental animals with sterile abscesses have confirmed this evidence of inhibited hemoglobin production and have brought to light profound disturbances of iron and porphyrin metabolism.[5] Serum iron falls promptly to low levels and before anemia develops, while serum iron binding capacity subsequently becomes sub-normal. In the established anemia, iron absorption is disturbed, but mainly the iron is diverted to the reticuloendothelial cells, especially of the liver and spleen, and to an unimportant extent to the site of inflammation itself. The peripheral red cells may contain many times the normal amount of protoporphyrin and the excretion of coproporphyrin becomes increased. Despite this suggestive evidence of a disturbance of hemoglobin production, hypochromia is rarely present and the circulating red cells are usually normochromic and normocytic or sometimes slightly microcytic. In man chronic infection does not greatly alter the usual normoblastic level of erythropoiesis in the bone marrow. However, some observers have noted a moderate increase in cellularity and an immaturity of the erythroid cells.[5] This is of interest in view of May's[79] recent report of the action of infection in producing megaloblastosis of the bone marrow in monkeys while on diets low in folic acid. Such changes could not be prevented by vitamin B_{12}.

Hemoglobin production in chronic infections may not be enhanced by even large amounts of intravenous iron.[5, 80] Probably a similar deleterious influence upon erythropoiesis exists in metastatic cancer and lymphoma which may be accompanied by a considerable degree of anemia without evidence of bone marrow involvement by the tumor.[73] The non-specific erythropoietic effects of cobalt can be demonstrated in these anemias[23, 73] as in those of chronic infection[81] and uremia.[82]

In uremia and in other conditions associated with chronic nitrogen retention, erythropoiesis is probably diminished but without significant morphological change in the erythroid cells of the bone marrow despite hyper- or hypocellularity of its myeloid cells unless the non-protein nitrogen of the blood is chronically above 150 mg. per cent.[72] The most prevalent erythroid cell is the polychromatic normoblast; and

these often show karyorrhexis of the nucleus but are not diminished in numbers. Some hypoplasia of normoblasts seems to accompany chronic glomerulonephritis. In acute anuria due to any cause there may be a selective but temporary decrease in erythroblasts.[83] The circulating red cells in uremia include few reticulocytes and few abnormally shaped forms and are usually normochromic and normocytic.

There is a definite correlation between decreased circulating hemoglobin levels and increased levels of nonprotein nitrogen above 40 mg. per cent.[72] The accompanying hyperplasia of myeloid cells and megakaryocytes suggests a toxic state but although increased blood phenols and indols have been suspected, they have never been clearly implicated. Protein deficiency, even when severe as in nephrosis, without azotemia does not cause anemia. Both experimental and clinical observations indicate that a hemolytic process is sometimes contributory.[84]

Mechanical interference with erythropoiesis: This results from inadequacy of the mass of erythropoietic tissue relative to the mass of circulating hemoglobin required for the maintenance of a normal circulating hemoglobin concentration. From what has already been said concerning the greater rate of erythropoiesis with anemic or other forms of arterial anoxia than with normal hemoglobin levels, it is clear that a given volume of erythroid marrow may be adequate to maintain a normal circulating hemoglobin concentration when the arterial blood is relatively anoxic, but not otherwise. This principle, as was pointed out some years ago,[85] now appears in fact to be the basis of the normal moderate decline in circulating hemoglobin levels during the first weeks of life.[86] At birth the normal erythroid cell count of the marrow is about 40,000, but by ten days it declines to only 2800 per cu. mm. After two or three months, it rises to about 25,000. The reticulocytes in the peripheral blood, initially at three or four per cent, fall sharply during the first ten days of normal extrauterine life. Undoubtedly this decline in rate of erythropoiesis is the most significant factor in the rapid postnatal increase in anemia of erythroblastotic babies. This is more clinically obvious with a relatively mild hemolytic process.

In small babies such as premature infants or twins, the decline of the circulating hemoglobin level occurs to an exaggerated degree. During the first month or two of postnatal life, a parallel decline of red cells occurs and is not ordinarily responsive to any type of therapy. This anemia spontaneously disappears after the third or fourth month of

life. Similar effects on red cell, hemoglobin and reticulocyte levels have been induced in experimental animals first rendered polycythemic by low atmospheric pressure and then permitted to breathe air at normal barometric pressure.[87] Recently the highly pertinent observation has been made that in the newborn cyanotic infant with congenital heart disease, erythroid activity in the bone marrow may not diminish, peripheral reticulocyte levels continue to be elevated, and the prenatal elevated hemoglobin level is maintained or even increased.[86, 88] The failure of the normal postnatal decline in hemoglobin to occur is due to the fact that the normally low oxygen tension of the capillary blood of the infant in utero does not, in the infant with a right to left intracardiac shunt, rise to the normal level with the establishment of air breathing at birth.

Later in life a progressive decrease in the mass of the erythroid tissue may be induced by encroachment of fibrous or bony tissue[89] upon the marrow cavities, or by invasion of the marrow by metastatic cancer or by leukemic cells.[90, 91] Under all these circumstances the characteristic peripheral blood picture can often be recognized by the considerable variation in size and shape of the red cells even when the anemia is slight. Moreover, nucleated red cells and less than mature members of the granulocyte series may circulate. These peculiarities are seemingly the result of local disturbances of erythropoiesis in the marrow. At any rate carcinomatous metastases in fatty or cellular marrow may be surrounded by a zone of active erythropoiesis containing primitive erythroblasts and normoblasts.[90] The additional deleterious effects of toxic inhibition of erythropoiesis in such patients[73] have already been discussed.

In various leukemias, although erythropoiesis is predominantly normoblastic, the presence of a few cells resembling the megaloblasts of pernicious anemia especially in the acute forms of leukemia, has been reported.[4] The cases of erythremic myelosis of di Guglielmo perhaps represent an even more exaggerated degree of erythroid disturbance in association with a less obvious leukemic process.[92] Vaughan[90] was the first to suggest that these changes in the erythroid cells might be the result of some type of local nutritional defect resulting from the competitive demands of the tumor or of the leukemic cells for essential red cell maturing growth factors. She emphasized the resemblances of the erythrogenic process in such patients to that of pernicious anemia. It is of interest, therefore, as already mentioned, that small but definite

reticulocyte responses to liver extract can be obtained in some patients with myeloid metaplasia. Elsewhere[3] the concept has been outlined that the frequent termination of polycythemia vera in a form of myeloid leukemia is possibly due to the fact that increased erythropoiesis was the first manifestation of the underlying leukemic process. Thus, it was suggested that the polycythemia resulted from a competitive deprivation of the erythroid marrow cells of sufficient oxygen to result in increased erythropoietic activity. At any rate, mild polycythemia has been observed to precede the development of recognizable leukemia of various kinds, sometimes by many years;[91] and the treatment with urethane of patients with established myelogenous leukemia and moderate anemia may cause polycythemia to develop—perhaps, unknown to the clinical observer—for the second time.[93]

Conclusions

It may be seen that normally erythropoiesis is the preoccupation mainly of the polychromatic normoblasts of the bone marrow and is a process under critical control probably by a humoral mechanism responsive to the amount of oxygen carried in the arterial blood. In response to a purely hemolytic anemia, the rate of red cell and hemoglobin production by the bone marrow may be increased many fold provided the essential building stones and catalysts for the construction of the hemoglobin and its ingenious and durable circulating containers are available. The predominant normoblastic erythropoietic cells become vastly increased and somewhat more immature, and with severe anemia may be increased in size.

As the result of but few specific nutritional deficiencies does erythropoiesis in man lag behind the normal rate of red cell destruction. Erythropoiesis may also be inhibited by toxic substances of external or internal origin such as aromatic compounds. These may permanently damage erythropoiesis or more probably some detoxifying process perhaps located in the liver. When so adversely affected, the bone marrow is more commonly hyper- than hypocellular, and some of its most immature erythroid cells may resemble the megaloblasts of pernicious anemia. Lack of hormones, especially those of the thyroid and perhaps the testis, slightly lowers the ceiling for circulating hemoglobin. The effect of the invasion of the bone marrow by foreign cells raises fascinating questions as to the local effects of such elements in depriving adjacent

erythroid cells of oxygen or of metabolites essential for their growth and development. Here again, certain erythroid cells may resemble the megaloblasts of pernicious anemia.

The erythropoietic capacity of the marrow in a given individual at a particular time can be evaluated only when the balance sheet of favorable and unfavorable factors upon red cell production is drawn up. Thus, for example, it cannot be expected that the bone marrow of the unborn child, though occupying all the bones of the body and maintaining a slightly polycythemic hemoglobin level, will continue to do this successfully after it is deprived of the stimulus of the anoxia of intrauterine life at the time of the establishment of pulmonary respiration. Under these circumstances, until the ratio of erythroid marrow to circulating hemoglobin mass has increased, anemia is inevitable. Likewise, especially in the rapidly growing child or in the presence of a hemolytic anemia, the inhibitory influence of nutritional defects or of infections is quickly apparent in reducing the circulating hemoglobin level.

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THE LOUIS LIVINGSTON SEAMAN FUND

The New York Academy of Medicine announces the availability of the Louis Livingston Seaman Fund for the furtherance of research in bacteriology and sanitary science. Nineteen hundred dollars are available for assignment in 1954. This Fund was made possible by the terms of the will of the late Dr. Louis Livingston Seaman, and is administered by a Committee of the Academy under the following conditions and regulations:

1. The Committee will receive applications either from institutions or individuals up to December 1, 1954. Communications should be addressed to Dr. Wilson G. Smillie, Chairman of the Louis Livingston Seaman Fund, 1300 York Avenue, New York 21, New York.

2. The Fund will be expended only in grants-in-aid for investigation or scholarships for research in bacteriology or sanitary science. Expenditures may be made for:

a. Securing of technical help.
b. Aid in publishing original work.
c. Purchase of necessary books or apparatus.

THE MEDICAL PROFESSION AND PUBLIC HEALTH PROBLEMS*

The Anniversary Discourse

CHESTER SCOTT KEEFER

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It is indeed an honor to participate in your anniversary celebration and to discuss the relation of medicine and medical care to the many social problems with which the American people must deal. At the start, however, I must first pay tribute to the distinguished role of The New York Academy of Medicine in analyzing those problems and in acquainting the medical profession and the public with the need to adjust medical education and medical practice so that medicine may keep pace with progressive changes in the social and economic order. Your series of monographs on Medicine and the Changing Order gives us the benefit of your many years of study of economic and social developments as they affect governmental health services, hospitals, dentistry, nursing, industrial medicine, and medical research.[1]

As one who only recently has undertaken study of these problems on a national scale, I can perhaps realize more than most physicians who are primarily concerned with the practice of medicine or the administration of a hospital department the complex roles and interrelationships of many different groups of health personnel, institutions, and agencies in promoting the health and welfare of people in the United States.

HEALTH NEEDS OF TODAY

Public health activities developed largely when specialists in sanitary engineering, bacteriology, immunology, and epidemiology joined forces with the medical profession to attack communicable diseases like cholera, smallpox, yellow fever, and typhoid fever—diseases that were not only a threat to the life of the individual patient but also hazards to the community as a whole. The interrelationships between the medical

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profession and public health authorities were close and relatively simple. The public welfare demanded prompt notification of cases of suspected infection, accurate laboratory diagnosis of the infective agent, quarantine of the patient and those with whom he had been in contact, attempts to trace and deal with the source of the infection, and intensive, relatively short-term treatment of the patient.

The noninfectious chronic diseases which now constitute our greatest challenge in the field of public health present far more difficult problems and demand more complex action. They are usually obscure in origin and undramatic in onset and in response to treatment. They require long-term, expensive medical care, and very often this care needs to be supplemented by retraining and rehabilitation to a new occupation or pattern of living. These conditions also almost inevitably bring in their train serious social and economic problems for the patient, his family, his employer, and his community. Prolonged sickness is the most potent cause of poverty.

To parallel our success in reducing the prevalence and severity of communicable diseases we must fight chronic illness on at least five fronts. 1) We need to develop new knowledge and techniques for identification of chronic diseases in their early stages. 2) We must discover and, if possible, eradicate the now obscure causes of such conditions as hypertension, arteriosclerosis, and nervous disorders. 3) We must assure the accessibility and availability of well-trained personnel and well-equipped hospitals and related institutions to provide adequate preventive, therapeutic, and rehabilitative services. 4) We must increase public awareness of the importance of health services to prevent, diagnose, and treat incipient disorders. 5) We must stimulate public willingness and ability to finance the research, training, and public and private health and welfare services required for prevention, case finding, and treatment of patients who can be restored to relatively good health, as well as for the long-term care of the convalescent or the infirm. This is a large order and an ambitious program for any community. It means, for example, assuring throughout the United States prompt and easy access to health services such as are available in the medical centers of this city, plus nationwide efforts to assure the utilization of those resources at a cost which the patient or his family can afford to pay.

We are all thankful that, in a country such as ours, this ambitious goal does not necessitate government edict or regimentation of any of

the health professions. It will be achieved if, as, and when people as individuals give as high a priority to freedom from debilitating chronic disorders as they gave to the conquest of typhoid fever and yellow fever. The goal, moreover, offers a satisfying and challenging role to all members of all the health professions.

Some Steps Needed

The United States stands in a high—and sometimes in the foremost—position when nations are ranked according to health resources and health status. Thus we have high ratios of physicians, dentists, and nurses to population and a high life expectancy. We have low infant and maternal mortality rates and low death rates from communicable diseases. When these relative measures of health achievements are contrasted with our comparative national position in per capita income, however, we cannot feel complacent. Our top position in purchasing power and in material standards of living shows that we have the resources to assure foremost rank in all comparative measures of health status. Within the United States, however, variations among States in infant and maternal mortality are sometimes greater than the differentials between the United States average and the averages of most countries of Western Europe and of Australia and New Zealand.

Our main problem, then, seems to lie in the organization and distribution of health personnel and other health resources and in the differentials among and within States and community groups in their ability to support and use health resources. In time, our genius for organization and administration of industrial production to manufacture and distribute goods at prices which most families can afford to pay will doubtless find a counterpart in equally efficient and economical distribution of health services. In time, also, the techniques of public education will be effectively applied in increasing the demand for preventive as well as curative health services. It will be a long, slow process, we all know, but one well worth undertaking even on a piecemeal and experimental basis. Let's see if we cannot single out some steps that will gradually bring us nearer to our goal for better distribution of physicians, better methods of organizing and coordinating health services, and easier methods of meeting the costs of health services.

Distribution of Physicians: A recent study shows the tendency for medical students from small communities to establish their practice in

such communities.[2] Analysis of data on private practitioners who had been graduated from American medical schools in 1935 or in 1940 indicated that 50 per cent of those who were practicing in communities of less than 10,000 population had formerly resided in places of that size. The smallest communities—those with less than 2,500 inhabitants—attracted nearly 28 per cent of the graduates who had been former residents of these small places, as contrasted with only 5½ per cent of the graduates who had resided in cities of 100,000 or more population. Greater efforts must therefore be made to attract promising young men and women from small towns and rural areas to the health professions and to make it possible for them to return to their homes to practice their profession. This step will require solution of many of the problems of financing adequate premedical education as well as the four years of medical school and subsequent internship.

It will also require increasing the facilities for practicing medicine of high quality in the less populated areas through wider distribution of small hospitals and their affiliation with large medical centers. Furthermore it will be necessary to give rural and small-town practitioners periodic opportunities for further study through postgraduate and refresher courses and observation of the work of professional leaders in teaching hospitals and outpatient departments. In short, the type of continuing education which your Academy offers through its Committee on Medical Education in lectures, clinical research meetings, graduate fortnight sessions, and conferences will need to be duplicated in many medical centers to provide a network of communications to all physicians in the United States.

Organization and Coordination of Health Services: At present, I am sure you will agree, greater efforts must be made toward integration of health services, not only to reduce duplication of services and costs but also to fill existing gaps in those services within each community. Services for individual diseases or for separate groups of the population are splintered among a multiplicity of voluntary and governmental agencies. Greater emphasis on the family as a unit rather than as a composite of infants, school age children, industrial workers, and aged parents or relatives or as separate cases of tuberculosis, diabetes, heart disease, or mental ailments would go a long way toward improving the organization of health services as well as the health status of the family. Such organization, moreover, could greatly extend the utilization of

preventive services and thus often forestall the need for expensive long-term treatment of chronic conditions.

The family doctor, of course, must be the center and the coordinator of these services. He must be the family health adviser and must provide the link between medical specialists and such community resources as public and voluntary health agencies. Lacking sound health counseling and continuing health supervision, people will wait for pain or other symptoms before asking for medical advice or care and then, in many instances, will go direct to a specialist who concentrates on the organ or disease which they believe, perhaps erroneously, to be the cause of their distress. When the practicing physicians of each community assume their full responsibility for leadership in the organization and integration of the specialist services and other health resources of the community, we shall have moved a long way toward meeting one of the most serious problems of the public's health.

Again I must cite The New York Academy of Medicine for its role in working on problems of the organization and integration of health resources of this city. Your Committee on Public Health Relations has set impressive guide lines for the operation of home care programs and establishment of affiliated convalescent and nursing home facilities within the City's hospital system.[3] All communities in the Nation need similar leadership by the medical profession in bringing diverse lay and professional groups together to work out sound relationships in health services and medical care.

Meeting the Costs of Medical Care: Many of a family's most severe and prolonged costs of medical care can be forestalled by greater emphasis on prevention and by continuing health counseling on the part of the family physician. Significant recent developments in preventive medicine and in health education are the techniques of mass screening for evidence of one or more chronic conditions. Often, after these screening tests, those who are unaware that they have diabetes or hypertension, or both, by referral to a physician for positive diagnosis and treatment, receive medical attention early enough to keep those conditions under control. The screening itself can be effective only with close cooperation between the medical profession and the community's health agencies, however. Research is needed to improve the precision of these screening tests. At the present stage of development, mass examination can merely point to suspicion of the presence or absence

of a condition. The tests must therefore be supplemented by exact medical diagnosis by physicians. Means must also be provided for follow-up of persons examined and at times for prolonged treatment. Moreover, efforts are needed to induce more people to take these periodic screening tests.

Private voluntary health insurance efforts provide another significant means of meeting the costs of medical care. These programs must be extended in coverage and range of services, however, if they are to bring a high quality of medical care within the purchasing power of all families in the United States. They will also have to provide opportunities for individual as well as group enrollment. They will have to place greater emphasis on preventive and diagnostic services than is typical of most existing programs, and they must provide for inclusion of services by physicians, nurses, and rehabilitation teams in the home of the patient. Until these services are included, the load on hospital resources will be stretched to provide services for insured persons which might as well or better be furnished in an outpatient department, a doctor's office, or the patient's home.

Another unsolved problem in the expansion of voluntary health insurance is the large volume of existing chronic illness among the aged and the infirm. To keep their costs within range of most subscribers, many insurance programs find it necessary to exclude preexisting health defects and to refuse enrollment of the higher age groups. With better integration of public and private resources for this group of people the quality and continuity of care can be improved, and, quite possibly, the total costs can be reduced.

Expansion and improvement of private voluntary health insurance will go a long way toward reducing the future problems of meeting the costs of medical care for all groups in the population. One can cite the analogy in old-age and survivors insurance. When that program started, public assistance had to carry the major load of income maintenance for the needy aged, the widowed, and the orphaned. As the insurance program expanded in coverage, as levels of benefits were improved, and as more and more people acquired benefit rights, the public assistance rolls began to decline. Now, for example, old-age assistance rolls are declining at a rate of 6,000 a month. On the other hand, the number of beneficiaries of old-age and survivors insurance is rising by 60,000 a month.

Future improvement in the benefit structure of the OASI program and extension of coverage to additional groups of employed and self-employed people will continue this process. As benefit rights accrue for more and more people in the United States, they, too, will be contributing to the future economic security of their dependents and they too will be protected against the threat of a penniless old age.

Consideration of these problems is in the forefront of attention in Washington. Analysis of the role of the Federal Government in medical care and in aiding States and localities to provide health and welfare services is in progress by many groups and agencies. Legislative proposals will be forthcoming, one can rest assured. Again, your Academy's studies on medicine and the changing order set long-range goals and give proposals for future action.

The Individual and His Health Status

Whatever the future may bring in specific Federal, State, local, or private programs to improve the health of the people of the United States, we can be sure that it will reflect public demand and, accordingly, the level of public knowledge of the need for that action. People in the United States are more health conscious and better informed on health subjects than ever before. Science writers for the press, radio, and screen bring promptly to public attention new discoveries in medical research and new techniques in medical practice. Your lectures to the laity are outstanding contributions to popular knowledge of the progress of medicine.

These and other strides in health information and education augur well for the future state of the Nation's health. In the last analysis, the Nation's health depends on the health knowledge and health practice of each resident of the country. The social and economic problems of public health cannot be solved by any panacea or any program or group of programs. The individual citizen is individually responsible for his own health by choosing his pattern of living, by intelligent use of available health resources, and by stimulating local provision and support of the facilities and services he needs. As citizens we all must increase and apply our knowledge of sound personal health practice. As physicians, as guardians of the public health, and as informed individuals we have the added responsibility of improving the health education of our patients, our neighbors, and all others with whom we come in contact.

In its interim report, your Committee on Medicine in the Changing Order said that efforts to cure the world of its ills by "massive" doses of social legislation were fraught with great danger. I subscribe to that opinion. The medical profession, however, cannot solve the public health problems of the day by ignoring them. Only by listening to the patient's description of his aches and pains and by sympathetic understanding of the reasons for the emotional, social, and economic symptoms of which he complains can the doctor help the patient find and pursue his own way to recovery.

Medical Care of the Future

We know from past experience that improvements in the medical care of the future can be achieved by more effective and more widespread application of existing knowledge of the cause and treatment of illness and of methods of distributing the costs. We cannot rest content with existing knowledge, however, but must continue without cease to search for new and clearer understanding of public health problems.

First, we need to know more precisely than at present the volume and severity and types of illness in various age groups, occupational groups, income groups, and geographic areas.

We must also learn more of the natural history of diseases and the influence of inheritance, nutrition, emotional and physical stress, and environmental factors on the cause and course of illness and the effectiveness of recovery.

We need research in human motivations for the pursuit of health to give us clearer guidance than we now have in helping people to keep well and in aiding the disabled and infirm to make the most of their potentialities for self care and self support.

We must also search for ways to improve our methods of case finding, diagnosis, follow-up, treatment, rehabilitation, and reemployment of those who suffer from chronic illness or handicap.

We must extend our knowledge of the best and most economical ways of caring for the aged and the chronically ill, so that short-stay hospital treatment, when needed, can be supplemented and extended through home care or care in nursing or convalescent homes.

Studies such as these will amplify our knowledge of the social and economic problems of public health and will improve our means of dealing with them. New knowledge acquired through medical research

in laboratories, in clinics, and in hospitals will give us new and improved methods of treating individual patients. Effective communication and teamwork among research workers, practicing physicians, public health specialists, and social scientists will, as in the past, open new and brighter horizons for the medicine of the future.

The Colorado Springs Conference on Preventive Medicine in Medical Schools[4] has presented a challenging goal for teamwork between private practice and public health. Preventive medicine is defined as consisting of five stages or levels. The first is promotion of health through health education, improvement of housing and other social and environmental conditions. The second is specific protection through immunization, prophylaxis, and removal of health hazards. The third is early diagnosis and prompt treatment through case finding and intensive therapy. The fourth is limitation of disability to interrupt the natural course of the condition or prevent death. The fifth is rehabilitation to forestall complete disability and dependence and to help the patient make the maximum use of his remaining capacities.

In the past, public health practice has tended to concentrate on health education and environmental sanitation, while diagnosis and therapy have been the chief concern of private practitioners and hospitals and clinics. Rehabilitation is a relatively new field of endeavor that offers increasing promise for the future, as evidenced by the extent to which it can reduce dependency and restore assistance recipients to the capacity for self care and self support. I am convinced that recognition of the importance and essential interdependence of each of these stages of prevention cannot help but unite all health professions and community agencies in joint efforts and effective teamwork in meeting today's and tomorrow's problems of public health.

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RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR CHARLES RAGAN: The panel this afternoon will be primarily concerned with the treatment of rheumatic fever and rheumatoid arthritis. I would like to introduce the members of the panel. Dr. Edward E. Fischel, Associate in Medicine, College of Physicians and Surgeons, Columbia University; Assistant Physician, Presbyterian Hospital; Dr. Duckett Jones, Lecturer in Medicine, Harvard Medical School, but who spends most of his time in New York as the Medical Director of the Helen Hay Whitney Foundation; Dr. Theodore Bayles, from Boston, who is the Director of Research at the Robert Breck Brigham Hospital, which is one of the few hospitals in the country which is concerned primarily with rheumatic diseases, and Dr. Joseph Hollander from Philadelphia, Associate Professor of Clinical Medicine at the University of Pennsylvania who is the editor of Comroe's "Arthritis" which is usually used as the bible in this field.

We thought it would be reasonable first to pose certain questions for discussion and then, since we cannot cover the whole field in this brief time, we will ask for questions from the floor and will try to answer them.

I would like to preface these remarks by saying that people dealing with rheumatic fever can talk a little more authoritatively than people dealing with rheumatoid arthritis. They have their differences of opinion which I hope will be aired this afternoon but they can speak with a little more authority than we can since they feel they have some concept of the pathogenesis of the disease and its relationship to the hemolytic streptococcus. In rheumatoid arthritis we have no concept of pathogenesis of any value and we are feeling our way more than striding down a definite path.

First I would like to ask Dr. Jones to talk about the prophylaxis of rheumatic fever, which in itself is considered the most important point in dealing with this disease at the present time and to include in this the prophylaxis of the acute attack, how to prevent an attack from developing and secondly, how to prevent a recurrence in a rheumatic subject over a long period of time. Dr. Jones.

DR. T. DUCKETT JONES: I think your remarks would indicate that the old saying, "the grass is always greener on the other side of the fence," is quite true. While I do think that perhaps we have more definite ideas of the pathogenesis of rheumatic fever than you do of rheumatoid arthritis, there is still a volume of ignorance and many things

we need to know. Prophylaxis, I am sure you are all aware, is based on the fact that the majority of observers and students of rheumatic fever are in general agreement that there is an association between Group A hemolytic streptococcal infection and rheumatic fever, which often occurs two or three weeks after such an infection.

Since the late thirties there has been accumulating a consistent body of information concerning the prophylaxis of recurrent attacks of rheumatic fever; this started, of course, with sulfanilamide and a number of articles have appeared and are in general agreement that repetitive attacks of evident rheumatic fever can be remarkably reduced by daily prophylactic doses of sulfanilamide. From our military experience it became evident that sulfadiazine would accomplish the same results, and being considerably less toxic it has become more frequently used than sulfanilamide. More recently and based on logic and inference, it has become generally accepted that penicillin is also effective as a prophylactic agent. Many believe that penicillin is somewhat more effective than sulfadiazine, although I doubt that this has been convincingly demonstrated. I believe there can be little or no question but that either an adequate daily dose or doses of sulfadiazine or penicillin will sharply decrease epidemic streptococcal infections in the recipient, and that this is an effective means of preventing evident rheumatic fever recurrences. Half a gram of sulfadiazine daily, appears to be adequate in a child up to 60 pounds in weight; for larger children and adults, this dosage needs to be repeated, totalling a gram daily. The daily dose of oral penicillin is less well established, but 200,000 or 250,000 units of buffered penicillin twice daily seem advisable at present.

The American Heart Association's Council on Rheumatic Fever and Congenital Heart Disease has recently provided an excellent statement concerning the advisability of prophylaxis, dosage, etc.. This statement has been widely publicized. However, many physicians have not yet accepted the evidence as to the advisability of using these prophylactic agents. Numerous dangers and disadvantages have been cited. I would like to state that it is my belief that the data are significant. Further, I believe that the danger of early death or progressive incapacitating rheumatic heart disease from repetitive rheumatic fever outweighs all possible disadvantages. It is to be hoped that some day we will have new knowledge obviating the necessity for these daily prophylactic measures.

In addition, it has been demonstrated that adequate dosages of peni-

cillin for ten days, if given soon after the onset of a streptococcal throat infection, will sharply decrease the development of evident rheumatic fever. This appears to pertain to both recurrent and initial rheumatic fever. Since one-third to one-half of epidemic streptococcal infections are subclinical and not detectable, it is inadvisable to rely on this as a means to prevent repetitive rheumatic fever. In a known rheumatic subject, daily continuous prophylaxis has to be given. Long-acting parenteral penicillin may prove effective and practical. I would hope that in general Dr. Fischel would agree with this, but he may have some pertinent remarks to make on that score.

DR. EDWARD E. FISCHEL: I think I would agree completely, Dr. Jones, with one or two perhaps irrelevant reservations which may be of interest, namely, that while penicillin may be as good, if not better, than sulfadiazine prophylaxis, sulfadiazine has been so effective that it would be hard to prove that anything could be more so.

We have had several break-throughs with sulfa resistant strains but it is not the problem that it was during the war experience.

The other thing is that if a prophylactic agent is to be continued for five or more years after an attack of rheumatic fever, one prefers to use a preparation that is inexpensive, that can be taken once a day, even less frequently would be more desirable, then sulfadiazine is somewhat better than penicillin in that respect. Of course, now Dr. Stollerman and others are studying the long-acting penicillins which are given by injection and remove completely the factor of patient cooperation from day to day. When one such injection is given, prevention is assured for two weeks to a month. However, this regime requires further study and evaluation.

MODERATOR RAGAN: I would like to ask Dr. Fischel, if there are any hard and fast rules concerning the criteria for the presence of rheumatic fever and criteria to determine the extent of disease activity, in other words, the severity of the disease.

DR. FISCHEL: Dr. Ragan, I think that we would not have time to go into the criteria for diagnosis. Dr. Jones has summarized these very adequately in the past and most people are familiar with the various phenomena which we associate with rheumatic activity. It is highly important today to recognize that once a diagnosis of rheumatic fever has been made in a patient, any manifestation of inflammation can be looked upon as a manifestation of continued activity. Thus six weeks

after a known bout of rheumatic activity, a simple rise in temperature is rheumatic activity until proven otherwise and that goes for abnormal sedimentation rate and other things.

On the whole most people will agree that in the absence of clinical manifestations in a patient who recently had obvious rheumatic fever by all the diagnostic criteria, the sedimentation rate, while not 100 per cent valid, with occasional false positive and false negative results, is the most reliable indication and the most simply done of the tests for continued activity.

MODERATOR RAGAN: *Dr. Jones, do you agree?*

DR. JONES: I would agree with these remarks in general, except I think there are no laboratory tests, the sedimentation rate and electrocardiographic changes included, which are more than presumptive evidence of active rheumatic fever. In other words, these findings occur in other and varying conditions and until the patient has other objective diagnostic findings, it is advisable to use them only as presumptive evidence of rheumatic fever. Certainly, you cannot make an original diagnosis of rheumatic fever on the basis of an abnormal sedimentation rate, even when associated with other non-specific findings often observed in the course of rheumatic fever.

MODERATOR RAGAN: *Could you say what you mean, in one minute, by a definite proved diagnosis?*

DR. JONES: I think our diagnosis rests rather empirically upon grounds of grouping and assessing the findings as they are observed in a broad clinical experience. Arthritis or arthralgia; carditis as indicated by the appearance of significant murmurs, increase in heart size, pericarditis, or the presence of congestive failure; subcutaneous nodules; erythema marginatum; and Sydenham's chorea, are the major diagnostic criteria. The occurrence of two of these makes a diagnosis of rheumatic fever certain.

Then there are the minor manifestations of the disease—which in conjunction with a definite rheumatic fever history or the presence of heart disease of the rheumatic type assume greater significance, especially with regard to the continuation of active rheumatic fever. These are fever, nosebleeds, precordial or abdominal pain, anemia, weight loss of unexplained cause, pallor, rapid sleeping pulse rates, and unexplained laboratory abnormalities, such as electrocardiographic changes, anemia, sedimentation rate elevation, C-Reactive protein abnormalities and endless others.

DR. FISCHEL: I would like to agree, Dr. Jones, with the reservation that we do know that in many instances we cannot diagnose rheumatic fever and years later are impressed by the fact that heart damage had occurred. Therefore, in any individual who has a recent history of a streptococcal sore throat, any manifestation of abnormalities several weeks later and of significant duration, warrants suspicion. I am not going to say it is absolute evidence of rheumatic activity but a physician should be concerned about those things.

MODERATOR RAGAN: Now let us go on. We have mentioned something about preventing an attack and how to decide what an attack is. *How do you treat the acute disease, Dr. Fischel?*

DR. FISCHEL: There seems to be some disagreement and this is not a comfortable position. We are now encroaching very much upon the realm of the unknown. The treatment of rheumatic fever has had many ups and downs in fashion. Certainly something like salicylate or aspirin has been used for over seventy-five years and with varying impressions as to its effectiveness, depending upon how it is used. The more spectacular advent of hormone therapy poses other problems. There are opinions pro and con as to the efficacy of these agents.

We have learned one thing by examining the reasonably well controlled studies of the past. They seem to indicate the efficacy of early treatment and prolonged uninterrupted treatment, no matter which of the three agents, ACTH, cortisone or salicylates is used. These are principles to be kept in mind,—early and prolonged treatment.

Which agent is better is a question requiring much study. As you know, a cooperative study is now going on in this country and in England and Canada under the auspices of the American Council on Rheumatic Fever and the British Medical Research Council. While the final analysis has not been made, I think most participants in the study are not aware of any startling or obvious major differences between the three agents being studied. There may evolve certain differences in the follow-up but during the acute phase of the disease there have been no marked differences, with the dosage schedule used.

MODERATOR RAGAN: *It is difficult to go into dosage schedules with the large volume of material we have to cover, but can you say briefly how much aspirin, how much cortisone or how much corticotropin can be used? The answer is, obviously, enough, but can you be a little more specific than that?*

DR. FISCHEL: As far as salicylates go, everyone's guess has to be reckoned with. Generally we like to give a rather large dose, 5.4, 7.2 grams orally to a 12-15 year old individual but if there is serious evidence of toxicity we always reduce the dose. We don't see any point in causing hyperventilation or extreme and disturbing tinnitus or the more serious symptoms of salicylism. This dose is given orally and we observe occasional gastric irritation and other minor upsets.

As to cortisone, we have used a schedule—other people are using other schedules—of 300 mg. of cortisone the first day, 200 the next two days and then drop down to about 100 mg. a day. With ACTH, we begin with 100 mg. the first day and drop to a maintenance dose of 50 mg. There are investigators who are using phenomenally high doses of cortisone. Danowski and his group in Pittsburgh particularly, with rigid salt restriction, by adding potassium and avoiding some of the major problems of hormone treatment, are using long continued high dosage of cortisone with what may be interpreted as satisfactory results,—although there is a question whether patients adequately treated with salicylates would not have fared as well. The duration of treatment seems to be more important. The age-old practice of stopping treatment to see if the rheumatic process is still active is rather dangerous. It certainly prolongs the period of obvious inflammatory reaction. We prefer to continue therapy as long as clinical evidence of activity exists and then at least several weeks longer.

With salicylates we have even kept it up for months after subsidence of all clinical evidences of activity.

MODERATOR RAGAN: *One last question, do you like to use a completely suppressive dose for all manifestations of rheumatic activity, including the sedimentation rate?*

DR. FISCHEL: Your question is designed to point up a difference between the cortisone and the salicylate treated group. We like to give as much salicylate as is compatible with no toxicity and longer than necessary for reduction of all clinical signs. With cortisone we are apt to run into more trouble after several weeks, particularly in adults, and therefore are not as anxious, after the initial period, to suppress every manifestation of clinical activity.

MODERATOR RAGAN: *You are going to add to that, Dr. Jones?*

DR. JONES: I would like to say that I am not quite as optimistic about the therapeutic efficacy of any of our present agents as Dr. Fischel seems

to be. There are several observers who are very enthusiastic about the new hormone therapies. Not having had much responsibility or experience with this therapy but being familiar with the study referred to by Dr. Fischel and having observed patients on various dosage schedules at the House of the Good Samaritan, in Boston, I may say that I am very skeptical of the unequivocal value of hormone therapy. We need further study and observation.

The evaluation of clinical trials is one of the most difficult fields in medicine. We do not yet know the full value of salicylates, after having used them for seventy-five or eighty years. It is obvious that any new therapeutic agents need extensive and controlled study before we learn much about them.

DR. FISCHEL: May I interject for a second? The salicylates have been used with the philosophy of stopping the drug as soon as possible, to see if the patient is still active. That perhaps added to the detrimental feeling about them that many people have. On the other hand, most of the enthusiastic reports for hormone therapy are coming from individuals who have not traditionally employed salicylates in prolonged dosage and that may explain some of the differences. I agree that we have had failures of therapy with all three agents and none of them is ideal.

MODERATOR RAGAN: *But they do do something, you admit that?*

DR. JONES: They suppress a good deal.

MODERATOR RAGAN: *Make the patient a little more comfortable?*

DR. JONES: Considerably.

MODERATOR RAGAN: So much for this. It is sketchy. I admit, but there are two rather important practical points which I wish Dr. Fischel would mention. *The first is: When do you get a patient with rheumatic fever up and the second: What indices to prognosis do you have for ultimate cardiac damage the first time you see the patient?*

DR. FISCHEL: There was a time when people with rheumatic fever were arbitrarily put to bed for long periods of time without regard to their clinical picture. We certainly do not like to get anyone up who has any sign of activity unless it be an adult who is perhaps less susceptible to heart damage and who has been in bed for several weeks without cardiac involvement and may have a persistently elevated sedimentation rate. We would like the acute episode to subside or become stabilized in a plateau. No one today is enthusiastic about ambulating children or adults who have obvious carditis until all signs of clinical inflammation

have subsided. As far as the prognosis, perhaps Dr. Jones may have more to say about this since the very admirable study of a twenty year follow-up has recently been completed by him and his co-workers. We all agree that manifestations of serious carditis, of fibrillation, or of congestive heart failure are not as favorable in estimating the outlook as simple arthralgia, fever and increased sedimentation type of rheumatic reaction.

MODERATOR RAGAN: *Before Dr. Jones speaks, I want to bring out one point. Do you stop aspirin before you get them up?*

DR. FISCHEL: We do not. This is probably contrary to tradition. We feel that we run into more trouble stopping aspirin and observe more often a recrudescence of activity. Therefore when a patient is clinically well for several weeks, depending upon the duration of disease previously and on the severity of the disease, we will go ahead and ambulate these people, perhaps even send them back to school after a month, or two, or three, after discharge, while still taking salicylate. In many instances we may be giving salicylate unnecessarily but we feel that we avoid rebound in a few and it is worth it.

MODERATOR RAGAN: *What would you like to say about prognosis, Dr. Jones?*

DR. JONES: Could I first say just a word about ambulation? I agree with Dr. Fischel except that if no appreciable degree of carditis has been present, I think it is safe to get these patients out of bed quite quickly after clinical symptoms subside. However, laboratory abnormalities may continue indefinitely and I certainly hope that we will not keep patients in bed indefinitely because they have a fast sedimentation rate or a long PR interval as the only evidence of probable or presumptive continued rheumatic fever. Many have been given protracted bed rest for such reasons, and perhaps to their detriment. I don't know whether you agree with that or not?

DR. FISCHEL: I do.

DR. JONES: I think the present program for children and young adults in Boston is usually and on the average about a third of the former period of bed care or institutionalization. Unless there is severe and protracted carditis, eighty to ninety days seem an adequate period of limitation of physical activity.

The prognosis is difficult to evaluate, as I have learned from observing rheumatic fever patients for more than twenty years. Unpredictability

as to the frequency or severity of repetitive rheumatic fever in childhood is especially disheartening. In the years past, 20 per cent of these patients died in the first ten years, and 30 per cent within twenty of onset—a high mortality indeed. I believe this is decreasing, though accurate data are unavailable. We are now seeing fewer repetitions of rheumatic fever, because of the application of preventive knowledge. Prophylaxis against streptococcal infection and the extensive clinical use of antibiotics appear to be influencing the outlook favorably. This is of vital importance in the education of patients and parents.

There are other features which seem important after the subsidence of individual attacks of rheumatic fever, especially when full growth or adult stature has been attained. Prognosis depends to a considerable extent upon the rapidity and completeness with which active rheumatic fever subsides, and the amount of evident residual rheumatic heart disease.

After full growth, irreversible extensive cardiac enlargement and valvular lesions indicate a poor prognosis. At present many such patients are being improved by cardiac surgery. In some, the improvement is miraculous. The criteria for surgery, the permanence of the improvement, and the influences on longevity are presently being evaluated. Even after successful surgery, a markedly altered myocardium, as indicated by permanent cardiac enlargement, seems to constitute a serious prognostic finding. Prophylactic and preventive measures seem to constitute the most immediate hope for an improved prognosis.

MODERATOR RAGAN: We will come back to rheumatic fever but we have gone over our time. I would like to turn now to rheumatoid arthritis.

As I said before, there is no known prophylaxis because we have very little idea about the pathogenesis. The diagnosis of this disease is fraught with a great many more difficulties than that of rheumatic fever and often when a rheumatoid or not a rheumatoid can set up quite a discussion. In the full-blown disease it is perfectly obvious. In the beginning of the disease and in the atypical patient it is extremely difficult to be sure with what you are dealing. The prognosis is widely variable. We used to have the idea that this was a fulminating, steadily progressive disease. With further long-term studies, we have come to the conclusion that many patients with what we thought was a progressive disease have subsided and lived with their deformities with very little manifestation

of what we call activity. In our clinic at least we feel that activity is best measured by how much the patient complains, which is not a very good objective criterion for the activity of any disease.

The treatment depends upon the prognosis of the disease and when we have so little idea about prognosis, setting up accurate schedules of treatment is extremely difficult and personal factors enter into this problem a great deal. It must be remembered that we have no cure and what we are trying to do is afford comfort and to palliate and prevent some of the ravages. Each thing you do to a patient with rheumatoid arthritis entails certain hazards and everything you do must be done as a calculated risk.

We will now start out with some of these programs. The first is complete nihilism, saying to a patient and to his family that there is nothing that can be done for him. This is still carried out in certain places, but it is not considered good medical practice at the present time. It is a perfectly safe measure because you have not done anything to harm the patient but it is, to me at least, not in keeping with certain oaths we take.

For many years the accepted form of therapy for this disease was supervised bed rest combined with measures of physical medicine, notably active and passive exercises, splinting and surgery of deformed joints and rehabilitation. In the first place, you cannot handle this disease as you handle a static situation such as a post-polio paralysis or cerebral palsy. This is a progressive situation which may change. You rehabilitate the patient to the point where one leg is fine and the other leg breaks down, and we are not dealing with the classical picture of rehabilitation. This regimen, I still maintain,—I don't know whether my confreres will agree—is the best form of therapy. We have, however, few facilities to carry out this form of therapy here or any place else except at the Robert Breck Brigham in Boston, and that is just a drop in the bucket. We have no staffs for handling such forms of therapy. It is tedious. It is trying on both the patient and the physician, and overhospitalization is one of its dangers. Continued bed rest, unsupervised, can be very hazardous. With accurate supervision and careful care of the patient it is a good form of therapy but is not feasible, particularly in New York.

We have no difference of opinion concerning salicylates. I don't think anybody dealing with rheumatoid arthritis will maintain that salicylates are not a good drug. Is that fair? At least these people here feel

that way. I have heard nobody say that it is not, that this drug is not part and parcel of the treatment of this disease. By salicylates we mean salicylates at regular intervals up to tolerance and our ambulatory patient tolerance is less than the patient on bed rest in the hospital who is being treated for rheumatic fever. Most doses amount to about ten grains or 0.6 gm. after each meal and at bed time, a total of 2.4 grams, or eight pills a day. The difference between aspirin and sodium salicylate is a question that can be argued but we are not convinced of a great difference. Enteric coating is obvious if the patient cannot handle plain aspirin, or an antacid, not sodium bicarbonate. One of the aluminum hydroxide antacids is generally used.

I thought I would dispose of certain points on the blackboard before we enter the real discussion. The first is psychotherapy. There is a great deal of discussion at the present time concerning the efficacy of psychotherapy as a therapeutic agent and the role of emotional trauma in the patient with rheumatoid arthritis. In fact, in some places it is considered a psychosomatic disease. I must say that all these studies have been rather uncritical and in the literature there are certain obvious features. Where the psychiatric workup is adequate one doubts whether the patient had rheumatoid arthritis. Where you are sure that the patient had rheumatoid arthritis, the psychiatric study is pretty poor. There is one exception to this and that is Dr. Ludwig's work at the Massachusetts General Hospital in Boston, but again he is the first one to admit that he has a small group of patients and in this disease, because of its vagaries, you need large numbers to be sure whereof you speak. In the first place, we do not have any idea what kind of psychic trauma will initiate this disease. Most enlightened people working in this field, feel that it is difficult to see how this disease may be initiated by psychic trauma. An exacerbation, however, may be started by such an insult as it can be by any kind of traumatic episode, from a broken bone to a severe attack of pneumonia. There have recently been several fairly well carried out studies which tend to show that the patient with rheumatoid arthritis is no different from the average anxious individual in this anxious world. They have anxieties which are similar to those of many other people. There is no particular personality pattern that we can detect. So much for the pathogenesis on this basis.

Psychotherapy of the disease has had a rather unhappy time. Most of the patients we have sent to psychiatrists have been returned with

statements that the patient was too fixed to be approached. Again Dr. Ludwig has felt that he has been able to modify the disease partially in a small number of patients but again the series is small. It is fair to say now that we just don't know. But it is hard to see how this disease can be initiated by such incidents while it is understandable that the disease can, once established, be made worse by such an insult. The safe procedure at the present time is to handle the patient as one would handle any sick person, with reassurance and attempts to straighten out these problems as they arise but deep psychotherapy has not been too effective, in our experience at least.

I have asked Dr. Bayles to dispose of vitamins and transfusions in a few words.

DR. THEODORE BAYLES: It is obvious that in dealing with rheumatoid arthritis, one must be a philosopher. Regarding vitamins, we have had some experience in this field at the Robert Breck Brigham and there is a good deal of experience around the country. I would say that provided the patient is taking a high protein diet and fruit and vegetables in the usual so-called good foods, there is little evidence that any of the vitamins will alter in any way the actual course of the disease. I might say in addition that vitamin D in high doses is toxic and has caused a number of deaths throughout the country. Everyone who has worked with arthritis has seen them and I think there is no justification for the large doses of vitamin D which are advertised in medical journals. Certainly the risks are much greater than the benefits.

In the extremely sick patient who is markedly anemic running a fever and unable to eat and even with aspirin seems unable to get over the hump, formerly and especially in England, small transfusions were advised, 250 cc. once a week or less often. We can probably discard this form of therapy by saying that while this is good supportive therapy, that is *all* it is. I have yet to see any evidence that repeated transfusions will alter the course of the disease but it may be good supportive therapy at certain times.

MODERATOR RAGAN: *Do you want to say anything about homologous serum hepatitis?*

DR. BAYLES: The risk involved in giving transfusions, or even one of them, is homologous serum hepatitis. It is impossible to detect or protect the patient from this complication, which adds up to a very real risk. The dividend that you get, a very minimum surely, of losing

the arthritis when the patient is jaundiced does not justify the risk in this case.

MODERATOR RAGAN: *A few words about gold.*

DR. BAYLES: I preface my remarks about gold by saying in 1939 I set out to prove that it was of no value and now I use it almost daily. I was not able to prove it was worthless. I felt that this peculiar French medicine was obviously no good and took some patients in the hospital and gave them a series of gold treatments as then advised in England. In Boston the climate is quite cold when you mention gold. As you well know, Dr. Bauer's group feels that it does not alter the course of the disease. I do disagree. I feel that it does alter the course of the disease and I will say the controversy has been going on since the fall of 1927 when the first two papers on gold therapy were published. I will describe the preparations simply by saying that colloidal gold in my opinion is absolutely of no value. The compounds put out by Merck or Schering, the 50 per cent gold compounds, thiomalate or thioglucose, are the effective medicaments.

Our method of administration is similar to that used at the Presbyterian Hospital in New York and in most clinics, 25 mg. once a week for two weeks and then 50 mg. a week. I feel that if you carry on with the 50 mg. once a week up to a total of about 1400 or 1500 mg., and get no effect, then you may assume that gold is not going to help this patient and not continue on endlessly. I have written here in my notes, "mode of action." I state that simply because I have been interested recently in a group of patients who have had what we have called, for lack of a better term, hypersensitivity reactions in the skin. We recently analyzed twenty of these patients who had skin rashes following gold and in this group the sedimentation rate was normal within two or three weeks. Fourteen out of twenty had a 100 per cent loss of their rheumatoid arthritis and when I say "loss," I mean I am greatly impressed by this phenomenon. We have therefore hypothesized, not that it is of great importance this afternoon, that perhaps patients who do well with gold have developed some hypersensitivity to it. It would explain the dichotomy perhaps, between the patients who do improve and the patients who do not improve at all and I must say that we all see patients whom you might just as well wave at as they go by as give them gold as far as altering the course of their disease goes. This is simply an observation on the toxic reactions which we hope to track down further.

Regarding toxicity, there are the immediate nitritoid reactions which we all see with injections and skin reactions of various kinds, which occur in about 5 per cent of the patients. The most difficult and discouraging things are the blood reactions,—agranulocytosis, aplastic anemia or thrombocytopenic purpura, and despite BAL, cortisone, splenectomy and all the other agents, I am sure that there are some patients who will die. The depressive aspects of gold therapy on the bone marrow are rare, which is extremely fortunate. Probably one in a hundred patients at most gets any reaction of this sort and most of them can be salvaged with BAL and cortisone. Kidney complications are rare in my experience. Some albuminuria, more than one plus, is a signal to stop treatment but kidney disease due to gold is very rare.

In order to follow these patients while under treatment, I think it is wise to do hemoglobin, white blood counts, platelet counts and urine examinations every two weeks. I am sure that you will be left holding the burlap at times even when you do this because the patient can have one of these serious complications between two sets of laboratory examinations.

There is one other facet to this rather cloudy diamond and that is the problem of whether you can hold patients in remission, once you get a remission, by giving maintenance therapy of gold. I would agree with Dr. Ragan on this, that the vagaries of the disease are such that I am unable to say whether we can or not. However, I labor under the impression that perhaps we can, at times.

MODERATOR RAGAN: *How about you, Dr. Hollander, do you want to add anything?*

DR. JOSEPH L. HOLLANDER: I would like to say that while the earlier enthusiastic results have not been completely substantiated by later well-controlled studies, gold still represents the first chemotherapeutic agent that I would employ in a patient with rheumatoid arthritis.

MODERATOR RAGAN: *Can you, in five minutes or three minutes, discuss cortisone and corticotropin? I think all we can do at this time is to give some idea of your indications for the use of these agents. I don't think we can go into the toxic reactions or the dose schedules or such.*

DR. HOLLANDER: We are now at the opposite swing of the pendulum. First we all had high hopes, and the public press led the way, that these were the ideal agents for the treatment of arthritis, rheumatoid arthritis particularly. We now realize that this is not so, that these agents neither

represent the ideal treatment, are not adequate treatment in themselves, nor in any event the treatment of choice for long term therapy in the ordinary case. Since we are now at the other extreme, we must realize that the truth lies somewhere in between. We must remember that we have to protect the patient from further stress, and carry through the regular supportive measures that Dr. Ragan mentioned. Cortisone is certainly not the first thing to utilize, which seems to be still the tendency among certain physicians today. We also may think of it in this way: It would seem that what digitalis is to cardiac decompensation may be quite analogous to what cortisone is to the rheumatic diseases. That is perhaps a little over optimistic but that is the best we can say about cortisone. However, before going any further, I will say that I am glad I don't have to practice rheumatology any longer without cortisone. If we think of it as we do of digitalis for cardiac decompensation, I think we can get a little better picture and a quicker picture of what we are driving at, that is, cortisone has no effect on the cause of the disease. It improves the patients functionally. It certainly palliates their complaints, but it does not stop the progress of the disease. In other words, if we use cortisone alone, particularly in large doses, we may literally be "putting a penny in the fuse box" and making the disease worse than it ever was. We feel that *small* doses, *minimal* doses, only just sufficient to maintain improved function and decrease the amount of pain, swelling, and so on, are optimal. We should not try to suppress the disease with cortisone or ACTH, but should give it in the minimal amount that will keep the patient working and happy. We also believe, in our clinic at least, that instead of starting with the traditional 300 mg. of cortisone the first day and then working down to about 100 mg., we should start on 75 mg. or 100 mg. per day and work down quickly to a minimal dose. In other words, give the patient relief, but don't try to suppress the whole disease process. It is our feeling too that ACTH in small doses may be quite valuable, particularly to interchange with cortisone. We no longer use the so-called rest periods, when the patients almost invariably relapsed to the previous state or worse. ACTH courses during treatment with cortisone may revive the adrenals. We have seen many patients who have seemed to slip with long continued cortisone, improve with ACTH, and then back on cortisone they hold the improvement. We have used this method more or less routinely of late.

ACTH is a very valuable adjunct in the treatment of gold toxicity.

We have used it routinely, in short courses, for this and have also given fairly small doses of ACTH in the treatment of the "serum sickness" type of allergic reaction that we sometimes see following use of certain drugs. By decreasing ACTH slowly before discontinuing we have seemed to help these patients greatly.

I have yet to see a patient with rheumatoid arthritis who has been *cured* by cortisone, or who has even had a really persistent remission thereafter. There is another reason why I think we should regard cortisone in arthritis as analogous to digitalis in cardiac decompensation. If we "cortisonize" the patient we must expect to keep on continuous administration. We should not start the patient on cortisone until he seems to be slipping in spite of all other more conservative types of therapy that we have.

MODERATOR RAGAN: *It is fair to say we don't know how long we can keep a patient on cortisone, until many years have passed. Do you want to add anything, Dr. Bayles?*

DR. BAYLES: I am not quite as enthusiastic as Dr. Hollander perhaps, because I have only treated the sickest patients with cortisone and I felt that it was very useful in rehabilitation, very useful in the severely ill patient, but now at the end of a little over four years' experience with this material, I prefer to think of it as an antiphlogistic drug with pretty severe toxic side effects, rather physiologic effects, because they are not side effects. I certainly hang on to aspirin and everything else for a long time before I start a patient on cortisone because I do agree once you start you have to stay with it and I have yet to see a patient go into remission while on cortisone.

MODERATOR RAGAN: Some of the questions that are arising we will discuss later.

A question from the audience asks us to discuss the use of hydrocortisone.

DR. HOLLANDER: I might mention in a few words that hydrocortisone by mouth or by parenteral injection has very little advantage over cortisone. We have seen a few patients, and they are the exceptions, in whom hydrocortisone has had a slightly better systemic effect than cortisone. However, with intra-articular hydrocortisone it has been fairly well agreed after a little over two years now, that this represents a fairly innocuous, helpful, local measure. We have now treated 852 patients with a total of 8,693 injections in our clinic. We find that we can palliate

the inflammation in a large number. About 85 per cent with rheumatoid arthritis receive temporary local palliation from this therapy. This palliation may be partial, and it may be of fairly short duration. Yet the relapse that follows is seldom, if ever, really worse than the previous state. We have been encouraged by that. Also we have eliminated, by only injecting a few joints at a time, the systemic side effects or physiologic effects of hyperadrenalism. If we find that a patient has too much inflammation in too many joints, this therapy is not used. Some patients with generalized rheumatoid arthritis have only one or two joints, such as the knee, which are incapacitating. For these we feel that periodic use of intra-articular hydrocortisone will be helpful. We seldom give it oftener than every two weeks. I will not try to answer the question about technique because that is answered in other publications, and as a matter of fact, Merck and Company have published and sent out a pamphlet to all physicians on the technique. We can say, however, that it is no more formidable than drawing blood from a vein or giving an intravenous injection. Once you get the hang of it, it is an easy office procedure. You must maintain asepsis, of course, and be aware of the anatomical relationships, and the fact that the injection must be in the joint space, to bathe all the joint surface, to be effective. The diagnosis must be established first.

The only really lasting adverse effect that we have seen following hydrocortisone has been the aggravation of tuberculous arthritis. We thought the patient had rheumatoid arthritis, on the basis of a single centrifuged smear and culture of the joint fluid. Later, biopsy showed us that this was tuberculous arthritis and although the injected joint showed some improvement after the injection, it became worse thereafter with dissemination of the tuberculous process. So it is important that we do not inject hydrocortisone in the presence of infection. We have seen only two joint infections as the result of the procedure, both of which luckily were very easily controlled by penicillin, both into the joint and systematically. Intra-articular hydrocortisone is a repeatable treatment. We can repeat it indefinitely. We have used it now on many patients over a period of more than two years. A fair percentage of patients who have received the injections into a pair of joints over a fairly long time, have seemed to hold their improvement over longer and longer periods before they require reinjection. The effective dose is small, so that we seldom need more than 25 mg. into a knee. Perhaps

if it is a very active swollen knee we will use 37.5 mg.

The technical difficulties of injection into the hips make the results worse there, but when we can be sure of accurate penetration, by aspirating fluid from the hip, our results are excellent. This treatment is helpful in very many different types of arthritis. I won't go into that because this discussion is on rheumatoid arthritis. It is only a little over two years that we have been using this method and it must stand the further test of time. Whereas it has been corroborated by sixteen other independent groups of workers that intra-articular hydrocortisone is effective, we still don't know if it is going to be the long term type of palliation that we want for our patients. We have seen no evidence of worsening of the joints, and yet the natural course of the disease, as observed in untreated joints as compared with the treated joint, is very much the same. It has helped the patients to carry on, helped them to go about their jobs and enjoy life more, and therefore we think it is worth while. In fact, several of my colleagues and I myself have received it for minor rheumatic conditions, and when you use your own medicine it has to be pretty good.

MODERATOR RAGAN: Dr. Hollander originally described the use of hydrocortisone, Compound F, intra-articularly, and it is now generally accepted that a beneficial effect follows its administration. The only quibble with his findings is the frequency with which injections are needed to produce the beneficial effect. This is a quibble because there is disagreement about it and some feel that in a patient with rheumatoid arthritis the beneficial effect lasts only very briefly. Others feel that it lasts longer.

The procedure of injecting joints repeatedly is a chore, but it can be done, and it depends upon the indications, as in all these forms of therapy, how much you want to do.

Our time is almost up. We have not much time to answer more questions but I think we have to discuss Butazolidin for a few minutes. There is one question: Please discuss the value of Butazolidin in the treatment of rheumatoid arthritis,—also its dangers.

This is a matter of opinion. Its dangers are obvious to anybody who has been reading the J.A.M.A. Recently four or five cases of agranulocytoses have been reported. It does lead to marked salt and water retention, particularly in elderly people and it has been associated with increased peptic ulceration.

Its value as far as we can tell is that it is a very potent anti-inflammatory agent in the scale, if you want to make a scale, between aspirin and cortisone. It is more potent than aspirin and less potent than cortisone. In the minor nuances of this field it is felt that it is a little more effective in Marie-Strümpell spondylitis than in peripheral rheumatoid arthritis. It is a hazardous drug to use and it should be used with caution. You cannot predict when you are going to get in trouble with it. One of the patients who died had a white count done every three days and in between the counts he died. It is a potent drug and again you have to use it when you think it is necessary. We cannot tell you when you should use it but remember it is potent and dangerous. You have to balance the risks against the usefulness of it in your own mind. That is as far as I can go.

Do you want to say any more?

DR. HOLLANDER: I want to say one thing, Dr. Ragan. We started 157 patients on Butazolidin at the beginning of our study. Only twenty-two patients are still on it. The balance of these were mostly cases of rheumatoid arthritis. Most of the patients who are still taking it are patients with gout, and practically all the others were stopped for either ineffectiveness or toxicity or both. In rheumatoid arthritis we found the effectiveness varied from a great deal to nothing. Those who didn't show much effect with it, you might as well stop within a week. The patients who didn't tolerate it well would often be the ones who improved and you would have to stop anyway. About 50 per cent of the patients with rheumatoid arthritis obtained some benefit with it but since it was so toxic we wondered and still wonder whether it is worth the risk. We only use it now in the desperate cases where we cannot find anything else to help.

DR. BAYLES: I agree. I find it is effective in only one out of six patients. Where it is effective it is better than aspirin.

MODERATOR RAGAN: *So much for what we have to say. We will answer a few questions if we can.*

You mention the strep throat. What other organisms are found in the average sore throat?

Dr. Fischel.

DR. FISCHEL: The organisms found in a sore throat are many and variable, depending upon the environment, the season, and the presumed pathogenicity of many organisms in an epidemic area. Dr. Rammelkamp

felt that in order to give a good penicillin treatment for a sore throat he should begin early before cultures have been accomplished by the laboratory. He took his cultures and gave penicillin and then either by culture or by antibody response showed that 85 per cent of his patients in Cheyenne, Wyoming, had a streptococcus sore throat. The other 15 per cent did not. This was in a large Army installation in an epidemic area and season, and the incidence in the ordinary civilian populations is probably much less. There are, however, many who would recommend that every presumed sore throat—and there are ways of distinguishing it clinically perhaps from coryza or bronchitis,—should receive penicillin treatment, the dangers of not giving it being greater than the dangers of giving it.

MODERATOR RAGAN: *One question has been asked which is extremely difficult to answer. I will try and do it myself. The question is: Define rheumatoid arthritis.*

As I understand, it is a systemic disease with involvement primarily of the joints which in the typical case is symmetrical, involving quickly the wrists, proximal phalangeal joints, occurring 60 per cent in women, with nodules in 15 per cent, generalized lymphadenopathy in 15 per cent and splenomegaly in 15 per cent. We don't have any idea about the pathogenesis and very little about prognosis. That is as far as you can go.

One other question has been asked that Dr. Jones might care to answer: If a good proportion of the attacks of rheumatic fever are subclinical, are you erring in allowing a patient to become ambulatory on cessation of signs of clinical activity?

DR. JONES: To begin with, I don't think we have any idea as to how many attacks of rheumatic fever are subclinical. The subclinical features I mentioned earlier were those observed in a known rheumatic fever individual following streptococcal throat invasion or infection. To answer the question though, it should be safe to say that we have little or no evidence which suggests that conspicuous physical restriction during periods of very low grade or non-specific laboratory abnormality in periods of rheumatic fever, appreciably influences the amount of residual heart disease developed in the near or remote future. When a person develops mitral stenosis, who has had rheumatic fever many years before and without further clinical attacks, we have no idea as to when subclinical rheumatic fever may have produced the obstructive lesion mani-

fested by the stenosis. I am not at all certain that the outcome or heart damage from minor or subclinical rheumatic fever activity, which may follow streptococcal infection, would be favorably influenced by protracted or intense physical inactivity. It would seem more pertinent to institute a prophylactic regimen and to hope that this would prevent subsequent rheumatic fever recurrences and perhaps some of the subclinical attacks. Would you agree with that, Dr. Fischel?

DR. FISCHEL: Very much so. During ambulation we don't stop observing the patient and if signs of activity do occur, as they have even during maintained salicylate therapy, we can always put the patient back to bed, feeling that we have not done too much harm.

MODERATOR RAGAN: *There are two questions here that might be answered very briefly. One is: What about the effects of antibiotics in rheumatoid arthritis? As far as I am concerned none has had an effect, including small doses of Terramycin. Is there any disagreement with that?*

DR. HOLLANDER: No.

MODERATOR RAGAN: *The second is with regard to the administration of blood from pregnant or postpartum women. Nobody has had enough experience with pregnant woman's blood. Postpartum plasma in most hands has been ineffective.*

A question—What about liver damage with gold? A series has recently been reported and no evidence of liver damage, including punch biopsy of the liver, could be detected following gold. Most of the liver damage with gold has now been ascribed to homologous serum hepatitis from contaminated needles.

There are several other questions.

DR. JONES: Could I make two practical suggestions about rheumatic fever prophylaxis? In statements about prophylaxis, it has been indicated that for oral penicillin to be effective it must be given forty minutes to an hour before meals or two or three hours afterwards. Recent information is to the effect that for oral use, buffered penicillin G tablets may be taken irrespective of meals. This will shortly appear in a report from the laboratories of Dr. Maxwell Finland of Boston. This removes one of the technical difficulties of administration.

The other suggestion concerns the early treatment of streptococcal infections to prevent recurrences or even initial rheumatic fever. Penicillin must be given in large enough doses and for long enough to kill

the streptococci. Ten days seems an adequate period. Otherwise, the organisms are merely suppressed and later reappear in the throat, obviating any preventive influences on rheumatic fever.

MODERATOR RAGAN: Dr. Hollander would like to make a statement about intravenous trypsin.

DR. HOLLANDER: We have been doing some work with trypsin to see if it would have an effect on the proteins of the blood, particularly, and incidentally whether it would bring about clinical improvement in rheumatoid arthritis. We have given four patients intravenous trypsin. We have found that there is a very definite fall in eosinophils following its use, which puts it in the same class as typhoid vaccine and other types of "stress therapy." There is some clinical improvement. It certainly seems to be, at least in our hands, not worth the candle because this is a difficult, rather dangerous type of therapy. I predict that it will never be a clinically practical one.

MODERATOR RAGAN: One other group in New York has arrived at the same conclusion.

On behalf of the Academy, I wish to thank the members of the Panel for participating in the session this afternoon and I hope that those who have attended will benefit from the discussion.

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HARVEY CUSHING AS WE KNEW HIM

Presented at a Meeting of the Section on Historical and Cultural Medicine, at The New York Academy of Medicine January 13, 1954

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HARVEY CUSHING AS WE KNEW HIM*

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TO RECREATE the life of a man either in a formal biography, or to portray some facet of his character in a brief paper, such as I have prepared for this meeting, is a challenging responsibility which, like matrimony, is not a thing to be entered into lightly. The presiding officer of this Section, Dean Curran, suggested the title which I am using tonight, namely, "Harvey Cushing as We Knew Him." In a formal biography one can hide behind the screen of more or less impersonal anonymity and relate the facts as disclosed in the subject's letters, diaries, and other papers. Dr. Cushing himself set a good example of this approach in his *Life of Osler*[1] for apart from evidence reflected in one or two group photographs one might read the Osler biography believing that Harvey Cushing himself had never known the man and had certainly never been close to him. Many reviewers criticized him for this stern impersonal approach, but I have always admired him for it and I tried to follow his example when preparing his biography.[2]

The title tonight calls for something a little more personal, and after giving a brief sketch of his life to orient any students who may be present concerning dates and chief events, I shall present some of my own reminiscences of the man drawn from a large file of letters which began in 1921 when I first went to Oxford as a Rhodes Scholar. At that time I was "Dear Mr. Fulton." I shall then say a few words about Dr. Cushing as a surgeon and follow it with an account of Harvey Cushing as a book collector. On the latter theme I am more competent to speak although I learned what little I know of surgery from him and have cracked many a skull of both chimpanzee and monkey following Cushing's techniques. My good man, Leslie Kerby—who should have been named Friday—came over with me from Oxford in 1930. He has, I

* Presented at a meeting of the Section on Historical and Cultural Medicine at The New York Academy of Medicine, January 13, 1954. Manuscript received February 1954.
† By invitation.

suspect, administered anesthesia to a greater number of subhuman primates than any man living, and having recorded everything I did in the operating room between 1930 and 1951 when I retired from physiology, he tells me that I have nearly three thousand operations to my credit during that period and only three or four losses from sepsis. I mention this not to boast but to indicate the extent of my indebtedness to a great surgeon.

A Sketch of Harvey Cushing's Life

The tenth child of a very busy Cleveland obstetrician, Harvey Williams Cushing—the name he received at baptism—was born on April 8, 1869. He died on October 7, 1939. Cushing came from a long line of physicians.[2] The first was David Cushing, Jr. who practiced at the end of the 18th century in the Berkshire hills of Connecticut and Massachusetts, and who died prematurely from typhoid fever contracted in line of duty. It was he who founded the medical tradition in the family. The family originated, however, from Matthew Cushing of Norfolk in England who arrived in this country in 1638. Cushing's grandfather was Erastus Cushing, a general practitioner, who took his family from the Berkshire hills via the Erie Canal and settled in Cleveland as one of the pioneers in 1835. Erastus' son, Henry Kirke, had a hand in founding the Medical College in Cleveland, later to become Western Reserve University, and he ultimately was appointed Professor of Obstetrics at Western Reserve. He was a stern old gentleman, especially stern with Harvey perhaps because two of his older sons had broken from the family and gone West, and when his youngest son entered Yale College in September, 1887, Dr. Kirke made him promise that he would not smoke, drink, be guilty of immoral conduct, or, worse still, join a college ball club or boat crew! The Spartan father sent Harvey an allowance once a month but it was never sent until Harvey had written to say exactly what he had done with the previous month's allowance.

I was able to reconstruct Harvey's four years at Yale and his subsequent five years at the Harvard Medical School and the M.G.H., where he interned, from a series of letters which he wrote home once a week to his father and mother, and which his father preserved in most systematic fashion. He always wrote separately to his parents, and one can only conclude, and I think with some justification, that neither parent

showed the letters to the other, such was the austerity that prevailed in the Cushing household.

Cushing's mother was a gay, warm-hearted and kindly woman, widely read and well educated, who occasionally sent him the odd ten dollars to use for some fun because she was quite certain that her husband rarely sent his son a penny to use for his own entertainment. I mention this family background because I think it accounts for Cushing's own austerity in later years, especially with his sons and daughters. He was not very liberal with them, never allowing the girls to smoke, but now and again, after they had become of age, in a moment of largesse he would give them an automobile or some other luxurious gift. He exhibited a curious mixture of penuriousness redeemed by moments of great warmth and generosity.

At Yale he probably did most everything his father had made him promise not to do, and he had an indifferent academic record until his last year when Professor Chittenden fired him with a deep interest in physiological chemistry and with the desire to go to medical school. Russell Chittenden was a man of keen perception and he saw that Harvey was a young man of unusual promise. Upon his graduation in 1891, Professor Chittenden offered him an instructorship in physiological chemistry, but by that time Harvey, having felt something of his family's tradition, decided to go on with medicine and he entered the Harvard Medical School in 1891 at the age of 22. He was a member of the first class that had opportunity for taking a four-year rather than a three-year course. His work in anatomy was so brilliant, his dissections so impeccable, and his artistic drawings exhibited such a degree of perfection, that he was put down unofficially by his instructors at the end of the year as one of the top men in the class. Professor Charles Putnam wrote before his death, "From the day his class was turned into the dissecting room, Cushing became as eminent among his fellows as he continued to be among his colleagues throughout his life." His performance in histology was similarly brilliant, and his notebook, which has been preserved, would be the despair of any student because of its finished drawings. While attending clinics he made sketches of the patients because he believed then, and continued to believe throughout his life, that the sketch would always convey more than the written word. Once when he was asked to pinch-hit in giving an anesthetic before the class, the patient, who had a strangulated hernia and was vir-

tually comatose, died on the table. This so upset him that he decided to give up medicine, but one of his wiser mentors dissuaded him from doing so.

After his tour of duty as intern at the M.G.H., during which time he had seen a number of instances of brain tumor in which the patient had died either during or following the operation, his interests became centered on this field of surgery, but it was several years before he had opportunity to take up the specialty because Halsted, on whose service he worked in Baltimore, was unsympathetic and felt that no able young surgeon should throw his life away on such an unpromising specialty.

Cushing had gone to Baltimore in 1896, and remained there first as Halsted's Assistant Resident and then as his Resident Surgeon until 1900 when he went abroad. It was during this first Hopkins period that he met William Osler who was to play such a large part in his later life. When he was first in Baltimore he was scornful of the slow-moving ways of the Baltimorians, and certainly things didn't move at the tempo of the M.G.H. where one had to move quickly in order to keep warm! His arrogance and impatience got him into trouble on more than one occasion in these early years, and it was Osler who finally reprimanded him. This occurred in March, 1902, after he had returned from Europe. Osler's two notes to him bear repetition:

"3 March 1902

"Dear Cushing: I arranged with Dr. Hurd—he did not understand that they were your private patients. He must have you put on the Hospital Staff in some way officially.

"You will not mind a reference to one point. The statement is made that you do not get on well with your surgical subordinates & colleagues. I heard of it last year & it was referred to by a strong admirer of yours in N. Y. The statement is also made that you have criticized before the students—the modes of dressings, operations &c. of members of the staff. This, I need scarcely say would be absolutely fatal to your success here. The arrangement of the Hospital staff is so peculiar that loyalty to each other, even in the minutest particulars, is an essential. I know you will not mind this from me as I have your interests at heart. Sincerely yours, Wm. Osler."

"Dear C. Do nothing of the kind! Who is free from faults—& failings! It is a simple matter—'Keep your mouth (as the Psalmist says) as it were with a bridle.' Your prospects here are A.1. & we need you. Yours ever, W.O."

I think these two letters should be framed and placed in the rooms of all interns, and perhaps, a little enlarged, in the more sumptuous quarters of Residents!

After his first four years at the Hopkins, Cushing went abroad and had a most profitable time working in Berne at the laboratories of Hugo Kronecker, the physiologist, and Theodor Kocher, thyroid surgeon, and later Nobel laureate. Before returning, Cushing spent a month in Sherrington's laboratory at Liverpool assisting him with some of his experiments on the higher primates, chimpanzees, orangs, and one gorilla, and in each instance he undertook the exposure of the brain and to make drawings exhibiting the excitable foci.

He returned to Baltimore late in 1901, and although he had started on neurosurgical operations before he had left in 1900,[3] he now settled down to follow the specialty in earnest. He began to study the surgical approaches to the pituitary, and his researches culminated in his well-known monograph on the pituitary which appeared in 1912 when he was able to record fifty cases (on most of which he had himself operated) and to give remarkably full case histories.[4] It was in this monograph that he set forth in detail his concepts of *hypo-* and *hyper-*pituitarism—a work that quickly won him world recognition.

In 1907 Cushing had been invited to take the Chair of Surgery at Yale. Because he was a loyal Yale man, the opportunity interested him, but after a year's consideration he eventually declined and wrote a long letter to President Hadley in which he stated that the reason he could not accept lay in the fact that the Medical School lacked a hospital with full-time beds for teaching and research, and that until it had such facilities the University would find difficulty in securing a man of the calibre it wanted. Hadley and the authorities in the Medical School were, no doubt, disturbed by Cushing's candor, but it was probably the best thing that ever happened to the Yale School of Medicine because it marked the beginning of the vast reform, begun in 1908 by another Hopkins man, George Blumer, which culminated during Milton Winternitz's tour of duty (1920-1935) as Dean.

After prolonged preliminary negotiations, Cushing was called to Harvard in 1912. He accepted, and took with him Lewis Weed and a number of others from among his more experienced assistants. He had a hand in planning the Peter Bent Brigham Hospital which was then in process of construction, but the First World War broke out before he had really organized the clinic, and he spent nearly three of the best years of his life dealing with cases of traumatic neurosurgery, first with the French and then with the British, and finally with our own forces. As one would expect, he did not spare himself, and by the end of the war he was a sick man with respiratory troubles and bad circulation in both lower extremities. However, he made a good recovery and between 1920 and 1932 he developed the greatest neurosurgical clinic of our time, training innumerable men from this country and from every other part of the world. He retired in 1932, and the following year we persuaded him to spend his retirement in New Haven where he had six good years—very happy years, I think—before his sudden death from a coronary attack in October, 1939.

Personal Reminiscences

First, may I mention how Dr. Cushing unwittingly, and before he had the slightest idea who I was, helped me get a Rhodes Scholarship. At Harvard between 1918 and 1921, I had concentrated in zoology and had become interested in endocrinology—indeed one of my first papers, published in January, 1921, had to do with the controlling factors in amphibian metamorphosis.[5] At that time the Minnesota Rhodes Selection Committee asked its candidates to prepare an essay which it might scrutinize. The theme of my essay had to do with the iniquities of neurosurgeons, such as Harvey Cushing, who operated on patients with endocrine tumors instead of more logically treating such cases with endocrine extracts. The Committee was duly impressed by this brashness and it sent me to Oxford where I might meet some wits sharper than my own. I don't know if I ever told Dr. Cushing this tale because I was a little embarrassed about it in retrospect, but that was how he helped me secure a Rhodes Scholarship.

It won't surprise you to hear that I have kept closely guarded every letter, and every scrap of writing that Cushing sent me. As indicated above, my first letter from him was addressed to "Dear Mr. Fulton." It is dated November, 1921, and apparently was in response to a naïve

letter I sent him out of the blue from Oxford saying that Lady Osler had given me access to Sir William's library, and that I would be glad to help in any way with his biography of Osler, verifying references, etc. The response was gentle and characteristic.

"November 16, 1921.

John Farquhar Fulton, Jr., Esq.
Magdalen College
Oxford, England

"Dear Mr. Fulton:

"I am so much obliged for your letter and am pleased to know that Lady Osler has put you in charge of the library. It is quite probable that when I come to Sir William's Oxford period I may wish to call upon you to authenticate some of the data which I have gathered together so hurriedly two summers ago. I am sure that when the time comes I will feel the need of checking up a good deal of the information which I then squeezed out of the library.

"With sincere regards, I am

Very truly yours,
s/Harvey Cushing"

I first met him in the flesh in June, 1922, when Lady Osler took me to hear his Cavendish Lecture on the meningiomas.[6] Lady Osler prevailed upon him to bring his tails and white tie because she well knew English custom, and also how much he despised formal dress! During the trip in 1922 when he gave the Cavendish Lecture, he also gave one of his reports on his brain tumor statistics. Up to May, 1922 he had had 780 cases of verified brain tumor of which 154 were pituitary adenomas.[7] Louise Eisenhardt, his assistant in pathology, kept his figures strictly up-to-date for the next ten years, and indeed even now she is keeping his mortality statistics for there are some 600 of his patients still alive. In 1922 his mortality rate was about 14 per cent because he had included all of his early cases. By 1931, when he gave his report on 2000 verified tumors, the mortality had fallen to 6.8 per cent.[8]

In 1923, while I was still at Oxford, Dr. Cushing began to write me at regular intervals inquiring about my plans, and insisting, among

other things, that if I were going to be a good physiologist, I could not get on without a medical degree and an internship. I took my Ph.D. at Oxford under Sherrington in 1925, and returned in the autumn of that year to enter the Harvard Medical School in the third-year class—this on Dr. Cushing's recommendation. I had already spent four years doing the things ordinarily done in the first two years of medical school. In retrospect I was not a very diligent student, but I managed to publish my book on muscular contraction in 1926 and graduated in 1927. Knowing that Dr. Cushing would excommunicate me if I didn't have a year's internship, particularly when he had offered me a place, I took the year 1927-28 for work on his service. He gave me complete freedom to do any physiological studies I chose on his neurological patients, and for a physiologist, indeed, for a neurophysiologist, this offered an unparalleled opportunity. Gilbert Horrax and I assisted Norman Royle in doing a sympathectomy on a patient with Raynaud's disease, the first therapeutic sympathectomy to be done in the United States.[9] The operation was carried out on Dr. Cushing's invitation. In the good tradition of British surgery, Royle exposed the patient's kidney with one dramatic slash of his scalpel, losing scarcely a drop of blood, and had the right lumbar sympathetic dissected and severed within about three minutes of the time he started while Dr. Cushing stood by somewhat horrified. After that, Royle backed out and left us to close the wound, which took some twenty-five minutes. This caused him great impatience; however, he thanked Dr. Cushing for the opportunity he had given him.

Cushing's letters nearly always had an amusing twist. Thus in 1926, in acknowledging a group of reprints which I had evidently sent him, he replied:

> "Thanks for your ipsilateral, decerebrate, myotatic, viscous, plurisegmental, contractious, inseparable, break-shocking and inhibitory communications. Since receiving the same I am conscious of the fact that the latent period of my skeletal muscles, at no time of the best, has been much increased, and that true latency and rigidity have been observed by my long-suffering secretary and others. With affectionate regards to your wife, I am
>
> Always sincerely yours,
>
> s/Harvey Cushing"

When occasion demanded, he could be both serious and inspiring. My wife and I were staying with Lady Osler at the time of her death in 1928, and in a hand-written note he thanked me for giving details of

> ". . . that marvellous woman's end . . . I am glad that you and Lucia could have come so intimately into the fold and so much later than the rest of us who are getting on in years. You will carry the memory and tradition of those noble souls longer now than any. Its a flame to be kept burning so long as possible.
>
> "Curiously enough it has always appeared to me as though W.O. was still here on earth so many things continued to emminate his spirit. So let us imagine that she too is still here and that the 'Open Arms' will remain as it has been for so many years a welcoming place of refuge, over which they continue to preside."

Harvey Cushing as a Surgeon

In the broad field of surgery Cushing was responsible for many innovations affecting not only neurosurgery but general surgery as well. The ether charts come first to mind.[10, 11] These he devised while still an intern at the M.G.H., with the help of Amory Codman, so that the anesthetist could make a continuous recording of pulse rate, respiration, and temperature. This was undoubtedly an outcome of the unfortunate experience he had had as a student when the patient he was anesthetizing died on the table. A few years later, after having seen the Riva-Rocci blood pressure cuff while travelling in Italy, he at once perceived that a continuous recording of blood pressure by the anesthetist, in addition to pulse and respiration, would be advantageous in appraising a patient's condition as the operation proceeded.[12] Cushing thus deserves the credit for initiating the keeping of continuous records during anesthesia, a procedure which is now used in all well-managed operating rooms throughout most of the world.

In the field of neurosurgery Cushing introduced a number of special operative approaches such as the transtemporal to the Gasserian ganglion and the transbuccal approach to the pituitary. In later years he often said that he kept body and soul together during his early years at Hopkins by operating on cases of tic douloureux for it was the only branch of neurosurgery in which, for some years, he had either patients or success.

But it was the problem of hemostasis in intracranial surgery that led him to some of his most significant innovations. He began with the head tourniquet,[13] an inflatable halo which occluded the circulation in the scalp areas above its points of application. This he abandoned when he discovered that surface bleeding could be controlled by injection of adrenalin solution into the scalp along the lines of the intended incision. At about the same time he found that the light tension created by light, pendant hemostats applied to the skin edge virtually stopped all bleeding from the scalp even without the use of adrenalin.[14] To stop hemorrhage from the bone, he used Victor Horsley's sterile bone wax, a procedure he had learned in 1900 while watching Horsley operate. In 1910 he developed the silver clip for vessels out of reach of the ligature.[15] At about the same time he began to apply small pieces of fresh muscle to stop capillary bleeding, and he also introduced suction for managing gross hemorrhage in the deeper cavities. With a sucker in one hand and a silver clip in the other, it is generally possible to arrest quickly any type of arterial hemorrhage. In 1915 he put two of his associates, Ernest Grey and Samuel C. Harvey, to work on the problem of developing a fibrin preparation that might be used to promote clotting.[16, 17] But even with all these ingenious devices, hemorrhage continued to remain a serious problem especially when highly vascular intracranial tumors such as the meningiomas and the hemangioblastomas were involved.

Electrosurgical Procedures: Off and on over the years there had been those who suggested that high frequency currents might be used to advantage as a hemostatic agent in general surgery, and as early as 1911 W. L. Clark had published a paper on "oscillatory desiccation."[18] Nothing much came of the attempts to use high frequency currents until the summer of 1926 when Cushing, after having seen a diathermy machine at Atlantic City cut up a large slab of beef, returned to Boston and sought the counsel of Dr. W. T. Bovie, physicist to the Harvard Cancer Commission, who at that time was developing high frequency circuits to aid in removing malignant growths in the body cavities, one of his circuits having been designed to cut tissue without bleeding, and the other to coagulate bleeding points. The first surgical trial of these new currents took place on 1 October 1926. In the presence of Dr. Bovie, who seemed never to have heard of asepsis, five coughing French visitors with colds in their heads, and a student blood donor who fainted and fell off his seat, Dr. Cushing removed a highly vascular tumor with

the cutting loop virtually without hemorrhage. On the basis of this initial success, he sent for all his patients with meningiomas which hitherto he had considered inoperable and began systematically to remove one huge tumor after another, an operation no other neurosurgeon would have dared to tackle.[19-21] Dr. Cushing was fifty-seven at the time this took place and, as Dr. Sam Harvey remarked some years afterwards, it illustrated "his alertness and aggressiveness in picking up a new idea."

But despite all these important technical advances, Dr. Cushing's greatest contribution to neurosurgery lay in the men he trained. Some of them are here tonight. At the time of the first operation with the Bovie unit, Leo Davidoff had just completed his year's tour of duty, and the late Hugh Cairns had begun his residency less than a month previously and the first Bovie operation was an early trial by fire. He was somewhat dismayed by the many-ringed circus which he witnessed during this operation, and wondered quizzically whether many of Cushing's operations were like that!

Dr. Cushing trained a host of other men who are now leaders in neurosurgery throughout the world. There have been many great surgeons, but few have had such a school of devoted followers—men who have carried his methods and traditions to the ends of the earth and who all take pride in being able to count themselves Cushing's pupils.

Cushing the Book Collector

Cushing's interest in old books and in books in general might be said to have been inherited in some measure, for David Cushing had brought together an unusual library for an 18th century practitioner, and Erastus Cushing also had a considerable private library. Henry Kirke, while not exactly a collector, did have a large collection of books relating to Benjamin Franklin, and he once published a paper in the *Johns Hopkins Hospital Bulletin* on the Franklin-Heberden inoculation pamphlet of 1759. His Franklin collection was bequeathed to Western Reserve Historical Society. With this family tradition, and under the stimulus of men like Welch, Kelly, and especially Osler, all of whom were collectors, it was but natural that Cushing should have been imbued with the desire to assemble a personal library.[22] A limited purse and a growing family did not permit much in the way of active collecting during his Hopkins years, but Osler, ever gracious, presented him with many of the cornerstones of what later was to become a great

library on the history of medicine, and Dr. Howard A. Kelly, one morning after a Vesalius meeting at the Johns Hopkins Medical History Club (1905), left a beautiful copy of the second folio of 1555 on his doorstep.

While recuperating from an appendectomy, Cushing designed a book-plate in the finest tradition of physicians' book-plates, doing the entire drawing himself. The design was sent to E. P. Dutton where it was given to E. D. French to engrave. Mr. French, a well-known book-plate designer, stated that he had never before had the owner design and draw his own book-plate.

Dr. Cushing's library grew little by little during the Baltimore period, and as soon as he settled in Boston in 1912 and had less to worry about financially, he began adding to his Vesalius collection and bringing together other important books on the history of anatomy. The war, however, interfered with all this, and there was little opportunity during the next four busy years to add much to his collection. He did, however, find in Madrid, on his way to France, the rare Spanish edition of Valverde with the Vesalian plates, published at Rome in 1556.

From 1920 onwards he collected in earnest, and beginning about 1925 he began to invest considerable sums each year in incunabula and others of the great rarities of medical literature. He usually made a note in each book of the place where he had bought it and what he had paid for it except in the case of the more expensive items whose price he made every effort to conceal. Miss Stanton, his secretary, has an amusing story about his copy of the Pietro d'Abano *Conciliator*, 1472, the earliest and one of the most beautiful books in his whole collection. When the bill came, he grabbed the envelope before anyone could open it, put it in his pocket, and sent the cheque in an envelope addressed by hand so that no one in his office would know what he had paid. Unfortunately, Dr. Cushing was away when the book itself arrived, and someone opened it. As there was no way of doing it up again in a convincing manner, Miss Stanton hid the book so that it would not be seen by anyone, and handed it to him on his return from a trip, not saying a word.

In 1933, having retired from the Chair of Surgery at Harvard, Dr. Cushing settled in New Haven where he was made Sterling Professor of Neurology. The following year when he went to Montreal for the dedication of the Montreal Neurological Institute, he saw the Osler

Library and what a large part it played in stimulating the students at McGill. Previously he had talked lightly of selling his library at auction so that other collectors might have the fun that he had had in bringing his own books together. After he had seen the Osler Library, his plans changed, and he decided, without consulting either of us, that the books of Arnold Klebs in Switzerland and mine, devoted largely to the history of physiology and neurology, should ultimately join his, provided the University would provide a proper building to receive them. I mention this because it resulted in making his collection activities more systematic for he became careful not to duplicate any books that Klebs or I possessed, and when the three libraries were eventually integrated, there was in fact very little duplication save for biographies, histories of medicine, and other secondary source materials. Dr. Cushing had brought together nearly 200 medical incunabula, and Klebs possessed all the significant reference literature of that period although he had only a dozen or so actual texts. Similarly, I had six or eight, none of which were duplicates. From then on, Dr. Cushing devoted his attention to rounding out his collection of early texts relating to the history of surgery and to his Vesalius collection, and when any one of the three of us bought anything important, we always informed the other two. Dr. Cushing also purchased a number of items I could not afford including the early Fernels and the first edition of Servetus' *De trinitatis erroribus*. In fact, he used to abuse me for being so cooperative in helping him spend his money!

My books were turned over to the University in 1940 or thereabouts. Dr. Klebs died in 1943, but owing to the war, the collection could not be moved, and it did not reach the Library until Christmas, 1946.

Several years ago I gave a somewhat lighthearted after-dinner address to the Harvey Cushing Society entitled, "On Being a Literary Executor."[28] I used to think Dr. Cushing had been rather hard on his loyal assistant, Gil Horrax, and on some of the others on his staff. However, when his will was read I took a deep breath because it turned out that I had been appointed his literary executor—he had never said a word to me about that! He had made a list of things he thought should be done with his collections and his papers: in the first place there was a clause saying that if Mrs. Cushing and his literary executor thought that a biography would be stimulating to students of medicine, $5000

should be set aside to help defray the cost of such an enterprise. I waited a decent length of time and then went to Mrs. Cushing with suggestions as to whom we might get to undertake such a biography. "Nonsense!" she said rather imperiously. "Literary executors always write the biography. That's why he appointed you." Then there was a request that his books be catalogued. This was done, and a short-title list was published in 1943. He also left an unfinished manuscript, little more than half completed, of a bio-bibliography of Vesalius. The literary executor was also to take this in hand. In addition there were to be annotated catalogues of some of his special collections. In other words, he left his literary executor enough to keep him busy for about twenty years! And I thought he was hard on Gil Horrax!

The funds for a new medical library at Yale were finally appropriated in the summer of 1939. At one point before this happened, the officers of the University had raised the question of whether it would be proper, war having broken out, to construct the new building just at that time. The question was put to him, and Dr. Cushing played his final trump card. "Very well, gentlemen. My books are going to Johns Hopkins." The architect's plans were not approved until the end of September, and several days later, while lifting a heavy Vesalius folio, Dr. Cushing had a coronary attack from which he did not recover, but while he was in an oxygen tent in the hospital, we were able to tell him that ground had been broken for the new building and this seemed to make him extremely happy. He died a few hours later.

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*Harvey Cushing As We Knew Him**

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Like everyone else who has had the opportunity to be associated with Harvey Cushing, I have often been asked what sort of man he really was. I usually find myself singularly inarticulate since I have frequently given thought to the matter and I am always a little surprised to find that I am likely to say something different about him than I had said before when asked the same question. He was a man of many parts and many moods, but hardly could he be called unpredictable because he could always be counted on to fit his mood and energies to the particular task confronting him.

If I were to mention but two things that left the greatest impression on me, one would be his ability to teach by example, devoid of the do's and don't's of the pedagogue. His attitude seemed to be "watch me and you'll see at least one good way to do it." But that he actually expected something more to develop from those who watched and learned was evident in his oft repeated remark that it is a poor teacher whose student does not surpass him.

The other quality was eternally diligent attention to detail without seeming to be petty or tedious. I recall hearing a discourse at one of our national medical meetings on how to write a medical paper, and the author began by saying few of us are endowed with the ability to write as freely and easily as a Cushing. This essayist could hardly have been aware of what pains Dr. Cushing went to in preparing a paper so it read freely and easily. I possess one of his manuscripts marked "third draft" which has every bit of margin and interspace filled with corrections and alterations so that it must have required at least two more drafts to begin to round into shape.

Rarely has a physician been so widely known or had such appeal outside his profession, and this brings me to my best story about him. I believe it was in the late Spring in 1933 when he was to sail from New York to Europe where he was to address the University College in London and then receive an honorary degree from the University of Paris. Richard Meagher and I asked him to come down from New Haven where he had only shortly moved from Boston, have dinner with us and be put on the ship which sailed at 9:00 P.M. So enjoyable was our dinner that we were all aghast to find that the time was a quarter to nine and we were on the upper east side of Manhattan—a long way from the North River Pier. But we started—knowing full well that some special action was required to avert disaster. The plan had evolved by the time we reached the most disreputable section on the west side; there were still five minutes before sailing time. While I went on with the Chief, Meagher got out to phone a plea for delay. That he had succeeded was evident when we arrived at the pier to find a well policed aisle through a gaping crowd to a single remaining gangplank. The Chief, sensing this drama, was not to be hurried and a cheer went up as the ship began to move out almost before he had reached the deck.

But the best part of the story is what happened in the west side bar where Meagher made a frantic call to the pier and warned the officials that there would be trouble if the ship sailed without the man who was father-in-law of President Roosevelt's son and the eminent professor of surgery from Harvard. As Meagher stepped from the open phone booth he was confronted by a shabby figure who said he did not wish to let a mistake go uncorrected, that Dr. Cushing was no longer professor of surgery at Harvard, but the new Sterling Professor at Yale.

* Presented at a meeting of the Section on Historical and Cultural Medicine at The New York Academy of Medicine, January 13, 1954.

*Harvey Cushing As We Knew Him**

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It would take more than ten minutes to describe Dr. Cushing as I knew him over a period of twenty years, and it is difficult to know where to begin. One of the memories that remains most vividly with me about him, was the tremendous intensity with which he conducted his work. The atmosphere was always charged. He had great power of concentration, which he focused in its entirety on the case at hand. While scrubbing for an operation, for example, he would be going over in his mind all the details in the case of the patient on whom he was about to operate, and anyone who addressed him concerning any extraneous subject, no matter how important, was rebuked by a withering glance, and received no answer.

On the other hand, when free from the cares of surgery he could be light-hearted and buoyant, even playful. I remember one occasion when we were working together on a rather long paper at his house. It was summertime and the family was away, so that the mènage was extremely informal. When midnight came and we were both very tired, and had decided to retire, he ran about the house, collected sheets and pillows to make my bed, drew a tub for me, and was distressed that he was unable to find a new toothbrush for me. He eventually scared up one that had been used, he thought, by Henry, but so long ago that he was quite sure "the bacteria must have all died off."

He was extremely reserved about personal affairs in relation to the residents, or at least to this resident. I remember one Saturday morning in April, 1926. He was committed to operate on a lady with a spinal cord tumor, and the operation went off on schedule. As soon as the tumor was removed, however, he turned to me and asked me to close the wound, even including the closure of the dura. This was most unusual, especially in a private case. When I got downstairs after the operation, I ran into Francis Grant who was spending a year with us as a voluntary assistant. Francis told me that early that morning Dr. Cushing's elder boy, Bill, had been killed in an automobile accident, but that the Chief did not want to disappoint the poor lady with the spinal cord tumor.

He never mentioned Bill to any of us after that, but later in the summer of that year he and I were still working on some papers. We were sitting face to face at two tables; his back was toward the door, and I was sitting so that I could see the entrance to the room. The family was in Maine, but young Henry, the second son, had gotten a ride down to Boston, and thought he would surprise his father. As I saw him in the doorway I was about to exclaim a greeting, when he motioned me to be quiet. He came up behind his father and covered Dr. Cushing's eyes with his hands. Of course no one except a member of the family would presume to have done such a thing. The Chief reached up, felt the hand of Henry in surprise, and exclaimed, "Oh, Bill." He immediately corrected himself, greeted Henry most cordially, and that was the end of the episode, but it was clear that Bill was very much on his mind.

Dr. Cushing's sense of humor has been well documented, and was certainly genuine if the proof of this is that a man appreciates a good joke even if it is at his own expense. He often liked to tell the story about Gus, the chauffeur and handyman about his house. Gus was a tall, lanky, taciturn Norwegian who performed multiple duties. Not infrequently when the Chief had worries about some case going wrong, Gus would

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find himself the butt of a severe reprimand, and one particular morning he was laced out for every sin of omission and commission in the Bible. Gus, who was at least a head taller than the Chief, looked down on his face intently without saying a word until Dr. Cushing had to stop for breath, at which point Gus interrupted, saying, "Excuse me, Dr. Cushing, but you have egg on your chin."

Dr. Cushing had an enormous sense of the dramatic, and very much enjoyed astonishing and mystifying people. I remember one morning going up the "pike" with him to make early rounds, and coming opposite us was a visiting physician from out of town whose signature in the visitor's book I had happened to witness the previous afternoon. Dr. Cushing nudged me and said, "Davey, who is that man coming toward us?" I gave him the visitor's name and home town, for the sake of the story, let us say it was Dr. Brown of Little Rock, Arkansas. He said nothing more until we came opposite the visitor, when he beamed him his most beguiling smile, clasped him in a warm handshake, and said, "Why, Brown, how have you been, and how is Little Rock?" Brown was speechless, but managed to gurgle a few inarticulate words in reply, and we continued on our rounds. That afternoon, Dr. Brown cornered me and explained almost breathlessly that he had been introduced to Dr. Cushing ten years ago at the time of the American Medical Association Convention in his home town, along with perhaps fifty other people, and how in the world he remembered him, and where he came from, was simply another expression of his genius.

Another episode exemplifying the same pixieish humor was the time when he had invited Dr. Chevalier Jackson to address the Harvard Medical Club. Preceding the meeting he had invited some twenty guests to dine with Dr. Jackson. At the last minute he received a telegram from Dr. Jackson that he couldn't be present for the dinner, but that he would be glad to address the meeting at 8:30. Dr. Cushing, nothing daunted, had a whispered consultation with Tracy Putnam, and the guests had a most enjoyable dinner with a bearded gentleman whom they all presumed to be Dr. Chevalier Jackson. They did not learn that they were the victims of a hoax until the time of the lecture when the real Dr. Jackson was introduced.

These are just examples of lighter moments in a life which was dedicated, in its every fiber, to the advancement of neurological surgery. During his tenure at the Peter Bent Brigham Hospital the little operating room where he did his work was literally and figuratively the hub of the universe in neurological surgery. His accomplishments have earned him the honor, respect, admiration, and affection of the entire world, and the pedestal upon which those of us, who were fortunate enough to be his students, had placed him.

*Dr. Harvey Cushing**

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I have often thought that one's personality was like a house with many rooms, some secret and some open to the public. No two people visiting this house would get quite the same impression. One's personality, like one's house, has little corners to which only the most intimate and trusted are admitted. When one considers in this light the personality of Harvey Cushing, it is obviously one of many facades and complicated internal architecture.

The public at large and most of those who worked in his environment were conscious of a rigid disciplinarian who ruled his colleagues, his assistants, his family, and most of all, himself with a very firm hand. Even those people who disliked him, and there were quite a few, admitted that no matter how heavy the task he set for his assistants, his own share of the load was always heavier.

I know of no better example of the saying that genius consists of the ability to take pains. Certainly, Harvey Cushing had an infinite capacity for taking pains. In the final analysis, his greatness consisted chiefly in the possession of this one faculty to an extreme degree. I, of course, did not know him as a young man. He was just sixty years old when I went to the Brigham Hospital, but at that time one was struck by his ability to work tirelessly day after day, being impatient with any interruption and willing to use any subterfuge to avoid recognition of a holiday. Although he accepted the fact that regular work was not to be done on Sunday, he was a firm believer in the six day week and happy if the urgency of a case forced him to schedule an operation on what he considered an unnecessary holiday, such as Decoration Day, Labor Day or the Fourth of July. Unquestionably this relentless drive to work dominated the picture of Harvey Cushing throughout his entire life and permitted him to achieve perfection in anything he attempted, even where natural ability was lacking. The existence of any lack in Harvey Cushing comes as a shock to a great many people, but it is nevertheless true that many of his greatest successes were arrived at only after laborious and tedious perseverence. A good example of this is in his writing. The finished product of his literary efforts was usually faultless, with continuity of thought, —but he did not write easily and the first draft was often clumsy, abrupt and even ungrammatical, requiring much re-writing and editing. When one considers how much writing he did in his life time, one's admiration for him must be increased by the realization that this writing did not come easily. One had only to watch Dr. Cushing operate to realize that here, too, this painstaking perfectionism made him indifferent to time and trouble and while his surgical technique was perfection of its kind, he lacked the speed and facility that characterized other leading neurosurgeons. In his living habits as well, he was the embodiment of consistency, determination and indefatigability; he exploited every talent that he possessed and exploited every opportunity that presented itself in the pursuit of his clearly envisioned goal, with a self discipline that never relaxed. These were the characteristics by which most people knew him.

In addition to these qualities which were responsible for his productivity, there were others which added color to his personality. There was a good bit of the showman in Harvey Cushing. He was very conscious of the strength of his profile and always maneuvred himself to be photographed from this angle. His sense of timing was acute and his dramatic sense made him able to win the heart of a little child patient or a large audience with equal facility. An excellent example of this occurred several

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years after I had left Boston. The occasion was the opening of the Montreal Neurological Institute at which Dr. Cushing gave the principal address. After the speeches were over, I left the platform and joined my newly acquired wife amongst the audience. At about the same time a long queue of prominent Montrealers had formed with the expectation of mounting to the platform to shake the hand of Dr. Cushing. He looked about the room for a moment and saw the long queue and also spotted me with my bride. Without a moment's hesitation he hopped from the platform, leaving the expectant people waiting with hands outstretched, and strode through the milling crowd, pushing people, including myself, aside to grasp the hand of my wife with the simple remark, "You must be Mrs. H., I'm so glad to see you." Needless to say, she retains a picture of him as the most charming man she has ever met.

In spite of his flair for the dramatic, artificiality was very distasteful to him. I remember well one spring afternoon at the Brigham when he was closeted for some time with a very conversational and stylish middle-aged woman, a possible benefactor of the Brigham. He had finally managed to terminate the conversation by piloting the lady in question by the elbow gently from his office and out the back door to her waiting car, but before he succeeded in depositing her into her limousine, a rose from the lady's corsage had been transferred to his lapel. Miss Stanton and I were watching the procedure from the window and were amused to see him wave goodbye to the car and with a smile which lingered until the car turned the corner, at which moment the rosebud was snatched from the lapel and stamped violently on the sidewalk.

Dr. Cushing's early training as an athlete made him conscious all his life of the importance of team play. He expected loyalty from the members of his team and he in turn was loyal to his assistants. That he demanded loyalty and expected understanding from members of his staff is well exemplified by an incident that happened to a senior surgical resident. A tempest in a teapot had arisen over a misunderstanding about the management of a patient on the ward. The patient was in the care of one of the junior surgeons on the staff who had requested a consultation from the dental surgeon. The latter not only saw the patient in consultation but proceeded to remove several teeth without further ado. The surgeon upon hearing of this made it clear that he had asked the dentist to look at the teeth, not remove them. He was so outspoken in his opinion about the matter that the dental surgeon was about to tender his resignation and went immediately to Dr. Cushing's office with this in mind, with the surgeon following along, still expressing his views as to professional conduct. As soon as Dr. Cushing sensed the situation, which he did very quickly, he put in an urgent call for the surgical resident and then busily engaged himself with some scribbling on his desk in order to appear occupied until the resident arrived. When the resident came breathlessly into the office, both innocent and unaware of the situation, he was met with a sudden tirade of abuse to the effect that he was being most delinquent in his duty as resident if he allowed two brilliant and conscientious young surgeons to become involved in a misunderstanding that certainly could have been avoided if he, as resident, were running his affairs properly on the ward and arranging for the necessary cooperation between the various attendings, etc. At about this point he was able to turn his head sufficiently to permit a hefty wink in the direction of the resident, who, being both perceptive and cooperative, smiled inwardly while the tirade continued until the junior attendings began to lose their starch and consider themselves fortunate in not being the recipients of such abuse. At this point Dr. Cushing thanked them for coming to him with their problem and they walked out of the room practically arm in arm and no more was said about the affair.

I must relate another incident that discloses an unfortunately obscure quality in Dr. Cushing's makeup. A letter had been received from the family doctor of a patient who had been operated upon a year previously for a brain tumor: the Chief asked me to look up his old record to see what had been done. It appeared that it had been a very large inoperable glioblastoma multiforme. The letter from the

doctor stated that the patient had been exceedingly well for about six months and had continued to run his business but that recently he had developed definite signs of tumor recurrence and was no longer able to go to his office. He added that the family was in rather dire straits with growing children, insufficient funds and a collapsing economic situation. I remember being greatly touched by the letter which Dr. Cushing dictated in answer to the doctor, somewhat as follows:

"I am terribly distressed to hear about the unfortunate plight of poor old so-and-so. Unfortunately, I am afraid there is nothing we can do for him. I would like very much to have had another go at the tumor and perhaps given him another period of useful activity, but in reviewing his records we find that such a possibility is out of the question. I recall that he paid me $500 for his operation and I will return a check for this amount which you may give him with the thought that it may help a bit."

I must admit that there were moments during my residency year when I did not look upon the Chief with the warmth and affection which now endears his memory to me. I remember distinctly sometime in March of 1931, when we were racing at break neck speed to complete the series of 2,000 verified brain tumors and when the tension of the service was added to by the fact that his big toe was giving him a great deal of pain. (It had not yet been amputated.) After a particularly trying morning when no one had done what they were supposed to do, and the case had proved to be a negative exploration with therefore no increment to the tumor score, we had all retired without lunch to the big room next to the brain room to examine several possible candidates for the next day's operation. In the course of this examination, the Chief put out his hand for my ophthalmoscope and, as was my wont, I tested the battery and then handed the instrument to him: unfortunately at that point the light went out. Much annoyed, he gave my favorite instrument several vigorous shakes, during which the head flew off and banged against the tile wall across the room. The day's activities had already made me feel about as happy as a political prisoner in Russia and a smoldering fury possessed me as I walked across the room, picked up the head of my ophthalmoscope, placed it back on the handle, tested it, found it worked satisfactorily and then replaced it in my pocket, ignoring his outstretched hand. After a moment's hesitation, I said to the nurse, "Get Dr. Cushing another ophthalmoscope." There was dead silence while we waited for an ophthalmoscope to be brought from the ward and nothing was said until the conclusion of the examination. It was customary at this point for the Chief to tell me what case to put on the schedule for the morrow thus signalling the end of our mutual activities for the day. On this occasion, however, he began to talk as he left the operating room for his dressing room. I, of course, had to follow in order to obtain the necessary information regarding the next day's case. He continued the monologue right into the dressing room and left the door open for me to follow which I did. He then began to change his clothes, talking all the while and gradually working round to the subject of how little he was appreciated by his residents. By this time he was tying his bow tie and I was then leaning against the wall behind him. The fire of my indignation pretty well burnt out, I had assumed a more relaxed attitude. As he adjusted his bow tie in the mirror he continued: "After all, this is a good opportunity and you should be able to put up with certain hardships for the value of the service, and," he continued, "I expect that you say lots of things about me and think lots of thoughts that aren't too complimentary, but the least you can do is have the consideration not to let me see you laughing behind my back." I realized then that he was looking, not at his tie, but smiling back at me in the mirror. This was about as close as he could come to an apology, but such moments were sufficiently appreciated to carry most of us through the long periods of tension and hard work.

As suggested in my opening remarks, the recounting of these little incidents in "my life with Harvey Cushing" may serve as intimate glimpses into the personality of this very great and admirable man. After the scholarly discourse you have heard presented by his biographers it would be inappropriate for me to attempt any comment on the importance of his work, or his influence on medical history. I only wish to say that, after my father, he has been the most important person in my small world. I shall always remember him with respect, admiration and a very deep affection.

*Harvey Cushing As I Remember Him**

JOHN E. SCARFF

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I know of no more pleasant assignment than to tell of Doctor Cushing's wonderful contributions to the development of the neurosurgical discipline, in the care of patients, and in the training of young surgeons; but I also know of no more difficult assignment than to attempt to tell you anything new after you have just finished listening to John Fulton, Bronson Ray, Leo Davidoff and Thomas Hoen discourse on the same subject. They have really given you already the meat of the matter, and there is left for me only to pass on to you a few of the crumbs which remain from this rich repast.

My own personal experiences with Dr. Cushing took place at a time when he was the master surgeon and I was a humble intern and resident. These personal experiences occurred during the daily routine of hospital life and seem incidental and disjointed. However, they are firsthand, personal and intimate experiences and they affected me at that most impressionable time when I was undergoing my resident training; and they were of inestimable value, as I see them now, in establishing my own standards for my work and for my relationship to patients. If the group here tonight will forgive me, I will address myself principally to the younger men in the audience who today are in their resident training years in the hope that they may catch, even secondhand, some of the inspiration which Dr. Cushing passed on to his residents.

One of my most vivid recollections of Dr. Cushing had to do with my first formal ward visit with him. On this occasion we visited the private pavilion to see a patient who had been admitted that day with a spinal cord tumor. When we entered his room, the patient was in bed and obviously in distress. Dr. Cushing swiftly approached the bed and threw back the bed covers, revealing the fact that this patient was uncomfortably perched on an old-fashioned bedpan. Dr. Cushing asked crisply how long he had been in such an uncomfortable position. The patient replied: "Perhaps twenty minutes or half an hour," But the patient was a nice man and added: "The orderly is very busy, you know." Dr. Cushing turned to me and said: "Scarff, we must help this man." I replied: "Yes, sir, I will go and look for the orderly." Dr. Cushing said: "Scarff, you will what? Are you above taking care of this man yourself?" Whereupon he personally cleaned the patient and washed him, and then took the bedpan in his hands and walked down the center of the corridor of the private floor to the utility room where he washed out the bedpan and hung it over the drier. When this was done, he turned to me and said: "Scarff, don't ever consider yourself too dignified to help a sick patient in distress."

On another occasion, after a long day in the operating room, about seven o'clock in the evening he sent for me and asked me to make rounds with him on the surgical wards. On one of these wards we came upon a poor patient who was just beginning to awaken from his anesthetic after a brain operation; he had vomited in the bed and was lying in the vomitus. It was a very difficult hour on the ward; the ward was full of sick postoperative cases; the dinner trays had to be cleared away; the day nurses were attempting to complete their reports before the night nurses arrived; and everyone was tired. The problems were more than the nurses could handle. Dr. Cushing sized up the situation very quickly and said: "Scarff, you and I will handle this matter." With that he went to the utility room, got

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a basin of warm water, some washcloths and towels, and some fresh linen and bedclothes for the patient. He then bathed the patient, dressed him in clean pajamas and changed all of the patient's bed linen, at the same time instructing me in how these things should properly be done.

On another occasion about the same time, while I was trying to pass a gastric feeding tube in an unconscious patient, I looked up to find him at my shoulder. He said: "Let me show you how this should be done to insure that none of the feeding gets into the windpipe of this unconscious patient."

On many occasions I saw him turn unconscious or paralyzed patients from one side to the other side. In such patients the legs usually lag behind the trunk and present a problem. He turned the patient so easily by flexing the knees and then using these as a lever. He was one of the most skillful bedside nurses that I have ever seen. His axiom was that every good doctor should be able to instruct the nurses how to do their work.

It was an interesting fact that Dr. Cushing personally did every dressing on every single patient on whom he operated, regardless of whether the patient came from a private floor or from the public wards.

Dr. Cushing's principle in the training of residents seemed to be that no fault or imperfection should go unexposed and unexploited by him. "This bandage is too tight, replace it!" "This bandage is too loose, replace it!" "This patient was allowed up too soon, put him back to bed!" "This patient has been allowed to stay in bed too long, we must get him up." But he invariably had a good reason which he gave me for these criticisms. Even when I knew that I had well performed assignments he had given me to do I can never remember him commending me for the jobs well done. Once, in a disgruntled mood I said something to him about this and in mock surprise and shock he exclaimed: "Why, Scarff! Why should anyone need to be complimented for doing his job well!" That was his philosophy of teaching his residents. It was almost as though he regarded his young associates as an old maker of Toledo plates regarded his metal, that one could only turn iron into steel by constant hammering and polishing, and this hard philosophy he never softened.

I remember well the electric charge which seemed to fill the air whenever he entered the operating room and then the calm which would eventually come once he was at work. And then I remember the little swagger with which he would leave the operating room after a job well done. It was the swagger of a natural athlete, and I am sure that he walked off the baseball diamond in exactly the same jaunty fashion after he had made an exceptionally brilliant in-field put-out for Yale.

Dr. Cushing spent every morning between nine and ten in his office writing letters to old patients. A stack of histories, pulled out of the files the night before by Miss Staunton according to some infallible system, was always awaiting him. He would deal with these charts in order and would write to each patient, ward or private, rich or poor, in the same intimate personal way. Often it was "Dear Bill" or "Dear Mary" and it would always contain such personal questions as "How is the strength in your right arm coming along?" or "Tell me about the vision in your left eye. Be sure to send me details or, better yet, try to come back and let me see you." When Dr. Cushing's patients did come back for follow-up, they never returned to the clinic; they always came to his office, and these afternoon follow-up sessions with old patients were almost like little social events or class reunions. Each patient was made to feel that Dr. Cushing was especially interested in him and certainly was his friend.

I remember the many delightful visits to the Cushing home in Brookline where we residents would be invited for Sunday dinner. When the weather was nice we would stroll around in the grounds to get the sun before dinner—often the only sun we would get for weeks at a time. I remember one amusing little game that Dr. Cushing played on several of these occasions. He had a trapeze bar in the old barn on his property. There were several of the younger residents and he would ask us all to write on a piece of paper the length of time that we thought we could hang by our hands from this bar, and he

proposed that we all place a dime or a quarter on the piece of paper. The one who hung closest to his estimated time was to take the pot. It is an interesting thing that Dr. Cushing knew just how long he could hang and invariably won the pot — and also an interesting thing that he could invariably hang longer than any of his residents. I am sure, however, that the dollar went to some useful cause, to buy tea and wafers for the laboratory where we always met with him in the afternoon, along with Louise Eisenhardt and Miss Stanton, for a few minutes to catch our wind and to "gather pearls."

At these Sunday dinners Mrs. Cushing and "the girls" were always with us. On these occasions Dr. Cushing would do most of the talking and would discourse at length about great historical events in medicine and great medical personalities of the past; or about the early history of the Massachusetts General Hospital or the early days at "The Hopkins." However, one thing was absolutely taboo on these occasions: There must be no mention of current problems then existing at the hospital. No one could ask, "What do you think about that new patient—" without being immediately stopped. This habit of Dr. Cushing of never permitting his social life to be contaminated by local and immediate hospital detail is amusingly told in this particular story:

I was very complimented to be invited to Dr. Cushing's home on his 61st birthday which fell on a Sunday, and I took out with me as a little gift for that occasion Emil Ludwig's new book "The Life of Napoleon." I was particularly intrigued by the book because the first half of it told of Napoleon's unique genius and his inexhaustible energies and reviewed his rise to power and world wide eminence; but the last half of the book told of his days on St. Helena when there was no outlet for his tremendous energies and where his world slowly contracted. I could not help but think of the impending parallel in Dr. Cushing's life when in a short year or two he would be retired by the age rule from the pinnacle of power and success to a life of relative inactivity. I left in the latter part of the afternoon having had a very pleasant day. The next morning when I came down to breakfast, I found two envelopes side by side in the mailbox. One was the familiar blue-gray of Dr. Cushing's personal stationery and the other was a plain manilla envelope. I opened the blue-gray envelope first and there was a very nice note from Dr. Cushing which went something like this: "Dear Scarff: It was so nice to have you with me on my birthday and I want to thank you for the delightful book you brought as a gift. I read the book through last night after you left — and got the point! Sincerely, H.C." In the other envelope was a terse command "Come to my office immediately!" and when I got there I was met by a machine gun account of things which I had neglected to do the *afternoon before* and which should be done immediately. The two notes — one warm and personal, and the other almost fierce — had been placed in the box at the same moment!

A small incident recalls Dr. Cushing's quick wit. On the occasion of his final retirement many of his former pupils met at the Brigham for a little farewell party, and at this time Dr. Elliott Cutler presented Dr. Cushing with a gift from us in the form of an old crystal and silver inkwell. Dr. Cushing thanked us with great feeling for the gift and then, quick as a flash, brightened up and said: "I get the significance also — for like the squid, you expect me to back away from the battle leaving behind a cloud of ink."

One final story about Dr. Cushing has long been a favorite of mine. It was told me by Dr. William McCallum, the great and beloved Professor of Pathology at Johns Hopkins, and one of Dr. Cushing's close friends, at a small dinner for Dr. McCallum in New York. When Dr. Cushing and Dr. McCallum were young medical men they had enjoyed a good holiday together in Paris and talked over their plans and hopes for their futures. At that time they said: "Let's meet in Paris ten years from now and talk things over." And they agreed that they should meet on the Fourth of July at high noon on the top of the Eiffel Tower. For ten years neither man ever mentioned the pact. But ten years later Dr. McCallum happened to be in Paris on July Fourth and thought that it would be great

fun to pay a quick visit to the Eiffel Tower and then, on his return to the States, to gently reproach his old friend for having failed to keep their ten year engagement. So he went to the Eiffel Tower a little before noon and took the elevator as high as it would go, to the top station where there was an observation deck and promenade. He spent fifteen or twenty minutes here walking around and looking out over Paris and enjoying the exhilarating sight. Then feeling he had made his point and would have some fun chiding Dr. Cushing when next he saw him, he started to leave. Some deep instinct, however, compelled him at this point to ask the guard if this was "the top" of the Tower. The guard said: "Well, yes, for all practical purposes, but there *is* a rickety iron staircase that goes up about a hundred steps to a small look-out — but visitors rarely go up there." Dr. McCallum's instinct stayed strong, and he decided to go on up to the top. Just as he got his head above the floor he heard a familiar voice say: "Well, Willy, I had almost despaired of your getting here." It was, of course, Dr. Cushing!

*Harvey Cushing As I Knew Him**

CHARLES BAGLEY, JR.†

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When I received a letter from Dr. Curran a few days ago in which was outlined the program of this meeting, I immediately accepted, impressed by the title of Dr. Fulton's talk, the talks by several other men, and Dr. Bronson Ray's movies. Certainly, no one is disappointed in what he has heard for each of us has had his memories of many years ago renewed.

It has been forty-seven years since my first association with Dr. Cushing, and it was then in the Sinai Hospital of Baltimore that I formed my first impressions of him. It is needless to say that they were strong impressions, and in him at that time I recognized that I was seeing something which I had not yet experienced though I had graduated in medicine three years previously.

There had been admitted to the ward of the Sinai Hospital a youth with evident intracranial disturbance, and Dr. Cushing was asked to see him. This was early in the period of his neurosurgical activities. Dr. Cushing was very thorough in his examination, and purely on the evidence of neurological disturbance made the diagnosis of cerebellar tumor. The day of the operation was set, and Dr. Cushing came across the street with a full surgical team and instruments. As resident of the hospital, I expected to be a part of the team but was told by Dr. Cushing that he was sorry but that his first duty was to the patient and that he could find no room on his team for one inexperienced in neurological surgery. So I was excluded, a fact which was not pleasing; but before the completion of the operation I realized that there was justification in Dr. Cushing's position and I was much impressed by the painstaking technique which he had developed. Although it was only seven years since the end of his residency under Dr. Halsted, he had been an Associate in Surgery for three years, at which time he had made his first report in neurological surgery in an address at Cleveland.

At that first meeting, therefore, I learned to appreciate his methods of diagnosis, his meticulous surgical technique, and his care and sympathy for both patient and family in a case which turned out to be a long chronic illness with a fatal outcome. In other words, I was at that time inoculated with what one might call "Cushingism" in diagnosis, operative skill, and postoperative care, which is so often necessary in the treatment of malignant tumors of the brain.

During the remainder of my residency at the Sinai, I followed rather closely Dr. Cushing's work at the Hopkins. At one time, he assigned me work in the Hunterian Laboratory, where his experimental work was done. When it was announced that he was to leave Hopkins and take up his work in the fall of 1912 at the Peter Bent Brigham Hospital, I followed closely his operative work in his last months at the Hopkins. At the completion of his last case, he remarked: "Now, Bagley, you can do these things. All you need is Davis." (Dr. S. Griffith Davis struggled with Dr. Cushing during his early days in neurosurgery to develop the anesthesia.) Until that moment, I had no idea of going with him to Boston, but I responded: "You don't want me to get into neurosurgery in such a haphazard fashion. Why don't you take me to Boston and teach me?," to which he replied: "This is a very sudden proposal." "But," said I, "not the first proposal." After some further discussion on the following day, he said: "All right, come along and I will see that you will get next to wounds."

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* Presented at a meeting of the Section on Historical and Cultural Medicine at The New York Academy of Medicine, January 13, 1954.

† By invitation.

This was in the summer of 1912, and he asked me to report at the Brigham Hospital in the fall. When I arrived with the rest of the staff, the administration building was just above the ground level. There was no place for neurological patients until Ward A was completed and occupied on January 1, 1913, and our time was spent in the laboratory of the Harvard Medical School. Dr. Lewis H. Weed was in this group and accomplished much in his cerebrospinal fluid studies. Dr. Cushing had apparently forgotten, but I think it was perhaps careful planning on his part, because on January 1, I found I had no appointment, a fact brought to my attention by Dr. Howard, the Superintendent. When this was mentioned to Dr. Cushing, he acted promptly and I was appointed in neurosurgery.

From that time to the end of the year 1913, I enjoyed the most pleasant association with him, for it was not long after that date that the work was thoroughly organized. As I recall, we had on the service an average of forty patients with major neurosurgical conditions.

What Dr. Hoen has said about Dr. Cushing's constant driving of the house staff was certainly true in those early days, but he drove himself to an even greater extent than he did the house staff, and his tendency to post operations on a holiday was certainly great.

For example, when the Christmas holidays arrived in 1912, though I had not been home since the fall, it was not until the morning of December 24, when Dr. Cushing apparently just conscious of the beginning of the holidays, arrived at the hospital and said during the course of the morning: "Bagley, I expect you would like to go home for Christmas." After the work was finished that morning, I left Boston and arrived at my home in Bel Air in time for Christmas dinner.

I am sure if at any time any group of men whom Dr. Cushing trained were to discuss him, the discussion would be very much along the line we have heard this evening. But an experience we had in the summer of 1913, which I will attempt to relate in not-too-great detail, stands out in my mind, as it exemplifies his ability to work long hours and accomplish what was so gratifying to him and all the members of his team and what would seem to be a task far beyond one's endurance.

Mary Ellen Shea, in her early teens, was admitted on June 2, 1913, having had headache since January, 1912. At the time of admission, she was completely blind, with marked evidence of internal hydrocephalus and unsteady gait. Cerebellar neoplasm was the preoperative diagnosis, and two days after admission the tumor was removed and proved to be a multicystic glioma. The tedious operation lasted throughout the morning, and at the completion a transfusion was imperative.

It had been arranged that the father be used as a donor, but he had not been hospitalized and a search for him disclosed that he was on the lawn of the hospital heavily under the influence of liquor. You recall that this was during the period of direct transfusion, as the citrated blood method which replaced direct transfusion was introduced by Lewisohn and Weil in the U. S. in 1914.[1] The donor was induced to come into the operating room, and his arm was prepared for suturing of the vessels for direct transfusion. His alcoholic state made the necessary cooperation difficult and necessitated Dr. Cushing's most persuasive powers. Though weary with the morning operation, Dr. Cushing, assisted by Dr. Emil Goetsch, the surgical resident of the hospital, succeeded in connecting the artery of the donor to the vein of the recipient, during which time I had finished the wound closure and was under the sheet with the anesthetist watching the then flickering pulse get weaker and weaker, the pupils dilate, and the respirations become very feeble. The anesthetist had followed her condition closely and now announced to Dr. Cushing that the situation was critical. About this time the blood began to flow and it being heavily charged with alcohol, Mary revived quickly and her first reaction was to start conversation with her very talkative father. The critical condition having passed and Dr. Cushing's patience being almost to the breaking point, he attempted to have the donor and the recipient cooperate until sufficient blood had been given to be worth-

while. Cooperation, however, was difficult to achieve. Finally, Dr. Cushing in vexed fashion, said: "Pat, everything is going all right but you must be still a little longer," whereupon Mary said: "Don't keep still for him, Pap, move all you want." Dr. Cushing then said: "Pat, if you don't keep still, you'll spoil things yet," to which Mary replied: "Don't keep still for him, Pap. Spoil it for him. Move all you want." By that time sufficient blood had flowed into Mary's vein to convince all present that the transfusion was going to succeed. The tension of the operating team was lessened, Mary's arterial tension had increased, and the operation was terminated. In the abstract of the history which I received recently from the hospital, there was a follow-up until December 16, 1926, at which time the note stated that Mary was apparently in perfect condition.

A follow-up from the Perkins Institutions and Massachusetts School for the Blind of Watertown, Massachusetts, for February, 1915, stated that the discs were pearly white, there was slight rotary nystagmus, and very slight pupillary reaction to light. She was seen again in May, 1926, in April, 1929, and in May, 1930, at which time the condition was the same.

I can truthfully say, as others have said before me tonight, that my days with Dr. Cushing were full with many rewarding experiences such as I have just cited, and the recollection of those days is still vivid and made more so by the happenings at this wonderful meeting tonight. One sees the same spirit abound here tonight that one saw when Cushing was here, as if he were now sparking the activities of this meeting as he was in the operating room at the Sinai in the spring of 1907. And I for one am particularly grateful for the influence of Dr. Cushing in 1907 and all the years since.

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*Harvey Cushing As I Remember Him**

EDWARD H. HUME

New York, N. Y.

These good former resident surgeons who have spoken tonight have the advantage over me in that they were actually staff associates of the great Dr. Cushing. I knew him, however, long before any of them did. Thus, in 1897-98, my first year in the Johns Hopkins Medical School, I was seized with a pain in my tummy one night and rushed over to the hospital to have the resident surgeon examine me. I was sure I had what the experts were calling intestinal obstruction. The resident surgeon, the first doctor I consulted through my medical course, proved to be Harvey Cushing. He sent me off feeling much better. I did not have intestinal obstruction.

In 1901-2 I was working in Liverpool with Sherrington, the physiologist and Boyce, the pathologist. During that winter Harvey Cushing turned up. He had been in Berne with Kocher and with Riva Rocci, and came to Liverpool for a brief period with Sherrington. We met daily at 3:45 P. M. for a cup of strong tea and for real professional fellowship.

The following year I was back in Baltimore, and gave ether many times for Harvey Cushing's brain cases. The feature of those administrations was that Cushing always insisted on recording of the pulse frequently throughout each operation. Severe? Yes, he was severe! But his was a kindly severity. Think of being initiated into sphygmomanometry by so distinguished a teacher!

Then, in the first World War, after America got into the fray, Cushing was the leader of the Harvard surgical unit that was lodged in a little village on the coast of France. The Harvard crowd set about indoctrinating all the French peasants! Yes, crimson was the American national color; yes, America's national hymn was "Fair Harvard, thy sons to thy jubilee throng!" Soon after a second American surgical unit arrived, and the French peasants poured down to the beach to welcome "Les Americaines." One peasant woman, well indoctrinated, snatched off a red petticoat and waved it up and down the beach, shouting "To Hell with Yale!"

Tonight, we have heard Dr. John Fulton's brilliant paper about Cushing. Perhaps we do not all recall that Sherrington tried to persuade Fulton to stay in physiology. Had he done so, he might well have become Sherrington's successor at Oxford as Regius Professor of Physiology. It was Cushing who finally kept Fulton in surgical physiology.

* Presented at a meeting of the Section on Historical and Cultural Medicine, at The New York Academy of Medicine, January 13, 1954.

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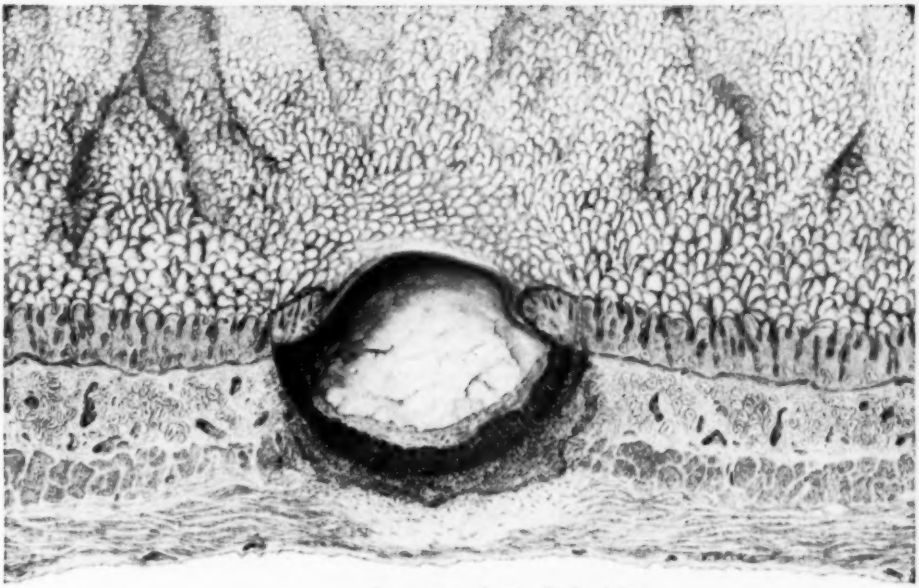

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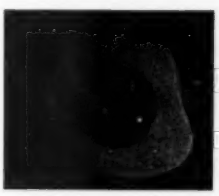

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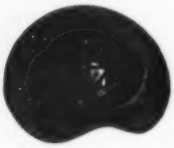

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November 18 CURRENT CONCEPTS IN THE MANAGEMENT OF ARTERIOSCLEROSIS—(Panel)—William Dock, *Moderator, Professor of Medicine, State University of New York, College of Medicine at New York City,* with David Adlersberg, Howard A. Eder, Forrest E. Kendall and Charles F. Wilkinson, Jr.

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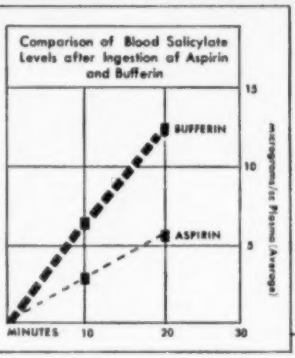

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1. Effect of Buffering Agents on Absorption of Acetylsalicylic Acid. J. Am. Pharm. Assoc., Sc. Ed. 39:21, Jan. 1950
2. Gastric Tolerance for Aspirin and Buffered Aspirin. Ind. Med. 20:480, Oct. 1951

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